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# ELECTRICAL STIMULATION AND NEUROMUSCULAR FATIGUE IN HEALTHY AND CHRONIC POST-STROKE POPULATIONS

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# ELECTRICAL STIMULATION AND NEUROMUSCULAR FATIGUE IN HEALTHY AND CHRONIC POST-STROKE POPULATIONS

by

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## Dedication

Forever and always, to Jodie, my love and my life.

Without you, none of this would have been possible.

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# ELECTRICAL STIMULATION AND NEUROMUSCULAR FATIGUE IN HEALTHY AND CHRONIC POST-STROKE POPULATIONS

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Neuromuscular electrical stimulation (NMES) has been shown to be effective for recovery of motor function following injury or pathology, however, NMES can impart rapid fatigue and the specific parameters of stimulation that maximize force output and delay the onset of fatigue remain unclear. Frequency, intensity, and pulse pattern are a few of the parameters that can be manipulated to achieve desired outcomes. Strong evidence supports the use of higher frequencies of stimulation to maximize performance of fatigued or paralyzed muscle. Likewise, several studies advocate the use of varied pulse patterns, rather than constant pulses, to maximize force output as well. Much of the research literature regarding NMES use with a pathological population involves spinal injured individuals. Much less is known about the effect of NMES on motor recovery, especially when delivered through varied pulse patterns, in the post-stroke population. The three studies contained herein addressed these issues. In Study 1, submaximal and supramaximal intensities of two variable frequency stimulation patterns and one constant frequency pattern were applied to the thenar muscles of a young healthy population. Results showed marked differences in force output between the two intensities. Submaximal stimulation enhanced the effect of the variable pulses and a greater force response was produced. In Study 2, the same three patterns were applied to the thenar muscles of a post-stroke group and an age-matched able-bodied group at submaximal intensities. Again, differences in force output were evident between the healthy and pathological group, and the variable pulses may have further depressed already weakened hemiplegic muscle. Study 3 compared the effects of a NMES rehabilitation program using a high (40 Hz) and a low (20 Hz) frequency to determine if task-specific improvements were related to frequency used. Results showed that those in the high frequency condition demonstrated greater improvements in strength, dexterity and force accuracy; those in the low frequency condition showed improvements in motor endurance. The results of this work suggest that the intensity, frequency and stimulation pattern of NMES used have a significant impact on the resultant muscle contraction and functional skills gained following stroke and should be carefully considered when implementing a clinical regimen for motor recovery.

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# GENERAL INTRODUCTION

Neuromuscular electrical stimulation (NMES) has been shown to be a promising option for motor recovery following paralysis (Daly & Ruff, 2000; Chae & Yu, 2002). NMES was first used clinically for gait assistance in 1961 (Liberson, Holmquest, Scott, & Dow) and since that time, much research has been directed toward determining how this medium can be exploited to facilitate motor improvement. While several studies have focused on the use of NMES with lower motor neuron lesions (i.e., spinal cord injury), less attention has been given to the use of NMES with upper motor neuron lesions such as stroke.

The application of electrical stimulation, however, presents challenges. NMES may recruit motor units in reverse order as compared to the order of recruitment during a voluntary contraction. NMES also results in synchronized and simultaneous motor unit firing, much unlike the asynchronous activity that typically occurs during normal movement (Baker, Wederich, McNeal, Newsam, & Waters, 2000). These conditions can increase the rate of fatigue development within the muscle.

Additionally, various parameters of electrical stimulation can be selected for use. Frequency, intensity, pulse width, and pulse pattern are components that can be manipulated to achieve desired outcomes. Because the selection of parameters will ultimately determine the effectiveness of the muscle contraction obtained, careful consideration of these variables is essential.

Continuous electrical stimulation patterns have been used frequently to investigate force output over time. An 80 Hz constant frequency pattern was applied to the adductor pollicis and caused greater force loss than a decreasing frequency pattern that began at 80 Hz and gradually declined to 20 Hz (Bigland-Ritchie, Jones, & Woods, 1979). Fuglevand and Keen (2003) investigated continuous stimulation at more physiological frequencies, finding that a continuous 30 Hz pattern sustained force better than a decreasing pattern that declined from 30 to 15 Hz. No force increase was seen as well when a 20 to 40 Hz pattern and a 40 to 20 Hz pattern was compared to a constant 20 Hz pattern administered to thumb adductors (Griffin, Jun, Covington & Doucet, 2006). This suggests that more complex stimulation characteristics, such as the incorporation of intermittent trains that change frequencies or pulse patterns, may be needed to prolong force output.

Intermittent electrical stimulation may be more effective in reducing rate of fatigue when compared to continuous stimulation. Intermittent stimulation uses a repetitive "on-off" sequence (e.g., 300 ms stimulation on, followed by 700 ms off) that may preserve force output. Loss of isometric force in the knee extensors was significantly less when stimulated with a 50-second intermittent 20 Hz pattern than when a continuous 20 Hz pattern was used (Spriett, Soderlund, & Hultman, 1988). Furthermore, continuous stimulation may result in a reduction of sarcolemmal excitation as expressed by a reduction in the M-wave amplitude (Griffin et al., 2006). M-wave amplitudes did not decline when an intermittent high (40 Hz) frequency stimulation protocol was used in the thenar muscles (Thomas, Griffin, Godfrey, Ribot-Ciscar, & Butler, 2003). Intermittent stimulation, with sporadic injections of "off" periods, may preserve sarcolemmal excitation thereby facilitating extended force production.

The force response of muscle will vary with different frequencies of stimulation. Robust evidence exists that there is a rightward shift in the force-frequency relationship of single motor units after fatigue, such that higher stimulation frequencies are needed after fatigue to produce similar pre-fatigue force levels (Thomas, Bigland-Ritchie, &

Johansson, 1991; Fuglevand, Macefield, & Bigland-Ritchie, 1999). The rightward shift also suggests that a progressively increasing stimulation frequency may assist in delaying the onset of fatigue and prolonging force output. Kebaetse, Lee, Johnston, and Binder-Macleod (2005) found that intermittent stimulation trains that began at low frequencies (20 and 33 Hz) and progressed to higher frequencies (66 Hz) were more effective in producing repetitive contractions from paralyzed quadriceps muscle than trains that began and remained at a high (66 Hz) frequency.

Electrical stimulation with doublets has also shown potential in optimizing force output. A doublet is defined as two rapid pulses of stimulation in succession with an interpulse interval of less than 20 ms (Simpson, 1969). Several studies have investigated the use of doublets during fatiguing contractions. Most tested brief trains of stimulation during non-fatiguing contractions and found that the trains with doublets produce significantly more force than trains without doublets (Cooper and Eccles 1930; Duchateau and Hainaut 1986; Macefield et al. 1996; Van Lunteren and Sankey 2000; Binder-Macleod and Scott 2001; Griffin et al. 2002) and that the force enhancement is even greater following fatigue (Bevan, Laouris, Reinking, & Stuart, 1992; Karu, Durfee, & Barzilai, 1995; Binder-Macleod, Lee, Russ, & Kucharski, 1998; Bigland-Ritchie, Zijdewind, & Thomas,. 2000; Ratkevicius and Quistorff 2002) and in paralyzed versus non paralyzed muscle (Griffin et al. 2002). A few studies used intermittent stimulation protocols to test the effects of repeated brief (300 ms) trains of electrical stimulation on force output. Some found that the use of doublets during intermittent stimulation was effective (Bevan et al. 1992; Bigland-Ritchie et al. 2000; MacIntosh and Willis 2000) but others did not (Binder-Macleod et al. 1998; Thomas et al. 2003). Kabaetse and Binder-Macleod (2004) found that during submaximal stimulation of the human quadriceps muscle of able-bodied younger adults, a constant frequency train that switched to a higher frequency train that included doublets produced greater force output than constant low (20 Hz) and high (40 Hz) frequency trains. Thus it is possible that a train that incorporates doublets will reduce the rate of fatigue and prolong force output over time.

Another parameter of NMES that has been less frequently examined is stimulation intensity. A submaximal stimulation level typically only activates a portion of the muscle fibers being stimulated; a supramaximal stimulation level recruits the maximum number of motor units during the contraction. Submaximal stimulation is usually better tolerated than the higher intensities that activate both motor and sensory fibers which can be interpreted by the cortex as painful or uncomfortable (Baker et al., 2000). Additionally, submaximal stimulation levels are frequently used with paralyzed or aged muscle because higher stimulation amplitudes may damage weakened muscle and demineralized bone (Hanchard, Williamson, Caley, & Cooper, 1998). Unfortunately, these lower stimulation amplitudes have also been shown to preferentially activate the largest and fastest nerve fibers, thus, when used, may not accurately reflect the contractile properties of the whole muscle (Preston, Venkatesh, Shefner, & Logigian, 1994). Godfrey, Butler, Griffin, and Thomas (2002) found that when sub- and supramaximal stimulation levels of NMES were administered to the thenar muscles of paralyzed individuals, submaximal intensities showed less relative force loss, force-time integral decline, and slowing of half-relaxation time following fatigue than did stimulation at supramaximal intensities. Therefore, continued investigation regarding the validity of using submaximal stimulation intensities of NMES to extrapolate the contractile properties of whole muscle is warranted.

Much research exists regarding the use of NMES with spinal-injured populations; far less research is available regarding the use of this modality with persons paralyzed by stroke (cerebral vascular accident, CVA). Stroke accounts for nearly 700,000 deaths per year and is the primary cause of long-term disability (American Heart Association, 2006). Chronic stroke survivors typically display sensorimotor deficits such as weakness, spasticity, paralysis, apraxias, or other limitations.

Paralysis of the upper extremity, and the hand in particular following stroke, creates a huge burden for stroke survivors. Motor dysfunction in the upper extremity following stroke reduces the ability to care for oneself, and the inability to handle and maneuver objects with the hand results in a major obstacle toward independent living. Recovery of the lower extremity is facilitated by limb loading and weight bearing (Brunt, Vander Linden, & Behrman, 1995); hand recovery is slower by comparison partially due to its somatotopic location on the brain surface and lesser representation in both hemispheres (Brust, 2000).

Because motor planning becomes impaired after stroke and participation in active exercise for rehabilitation is extremely difficult (Chae et al., 1998), alternatives to active exercise are critically needed. NMES can facilitate muscle contraction in paralyzed tissue to enable participation in rehabilitation programs.. From a clinical perspective, the optimal parameters of NMES for motor recovery in the hemiplegic hand following stroke are unclear. In a recent review of several clinical trials, frequencies used for clinical applications ranged from 25 to 50 Hz (deKroon et al., 2005). Because the ultimate goal of electrical stimulation used for rehabilitation purposes is muscle contraction, parameters that will facilitate tetany and generate sensorimotor feedback through excursions of movement have the potential to stimulate motor learning and recovery. Higher frequencies of stimulation have been suggested to increase cortical excitability (Pitcher et al., 2003), while the use of lower frequencies (20 Hz) applied to wrist and finger extensors was shown to increase functional grip in hemiplegic adults (Powell, 1999). Further examination of the effect of various parameters on motor outcomes is therefore warranted.

Improvement of motor skills following stroke can be facilitated with comprehensive rehabilitation but specific strategies and techniques that optimize return of muscle activity have eluded researchers for years. Aggressive and focused inquiry into methods that will improve motor function, promote permanent recovery, and return individuals to productive living are desperately needed for the advancement of clinical treatment strategies and for the development of neuroprosthetic systems and assistive devices.

## RATIONALE

Electrical stimulation characteristics that incorporate variable frequencies and the use of doublet pulses show promise for extending force output over time. Comparisons of intensities and frequencies in able-bodied and post-stroke populations can contribute to more effective rehabilitation regimens for the hemiplegic hand. Identifying stimulation patterns that prolong force output while delaying the onset of fatigue in paralyzed muscle is a critical element in developing clinical interventions that maximize motor return and in designing neuroprosthetics that can assist paralyzed individuals in successful task performance.

## PURPOSE

These investigations addressed the above issues by administering a variety of functional electrical stimulation patterns to the thenar muscles of able-bodied and chronic post-stroke individuals and examining the associated force output, fatigue responses and functional changes. Younger able-bodied subjects provided baseline healthy-normal data, and older able-bodied adults served as a model for the post-stroke paralyzed subjects, most of whom fall in the older adult category. No previous study has examined the motor outcomes in these populations using the stimulation patterns proposed. It was therefore the purpose of Experiment 1 to compare variable frequency stimulation patterns administered at submaximal and supramaximal intensities in a group of young able-bodied individuals to determine if force outcomes differ when varying intensities of stimulation are used. The purpose of Experiment 2 was to compare the force and fatigue outcomes of variable stimulation patterns in a chronic post-stroke and an age-matched healthy population The purpose of Experiment 3 was to compare high and low electrical stimulation frequencies delivered as a rehabilitation regimen for functional motor recovery of the hemiplegic hand in chronic post-stroke individuals.

## HYPOTHESES

The specific aims of these studies were to 1) investigate the impact of two intensities of variable and constant stimulation patterns on force output over time in the thenar muscles of a group of able-bodied participants, 2) investigate the effects of variable and constant stimulation patterns on force output over time in a chronic post-stroke population and an aged matched healthy older population, and 3) to test the functional outcomes of a high and a low frequency electrical stimulation rehabilitation program used for the hemiplegic hand in chronic stroke survivors.

**Study 1: Variable Neuromuscular Electrical Stimulation: The Effect of Submaximal and Maximal Intensities**

**Aim 1**: To determine if variable frequency stimulation patterns that either increase in frequency or that contain doublets will improve force output over time compared to constant frequency stimulation patterns.

Hypothesis 1. An intermittent 20-40 Hz increasing frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of young healthy individuals.

Hypothesis 2. An intermittent doublet frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of young healthy individuals.

Rationale: Higher frequencies will be needed as muscle fatigues; variable stimulation patterns preserve force output.

**Aim 2**: To determine if there is a difference in force output over time in the thenar muscles of young healthy individuals when stimulated at submaximal compared to maximal intensities.

Hypothesis 1. Increases in force output over time during an intermittent 20 Hz frequency train will not differ when stimulated at submaximal vs. maximal intensities

Hypothesis 2. Increases in force output over time during an intermittent 20-40 Hz increasing frequency train will not differ when stimulated at submaximal vs. maximal intensities.

Hypothesis 3. Increases in force output over time during an intermittent doublet frequency train will not differ when stimulated at submaximal vs. maximal intensities.

Rationale: Stimulation of a portion of the motor unit pool (submaximal stimulation) should result in fatigue effects that are similar to and representative of the effects when the entire available motor unit pool is stimulated (maximal stimulation).

**Study 2: The Effect of Variable Frequency Trains in Post-Stroke Hemiplegia**

**Aim 1**: To determine if variable frequency stimulation patterns that either increase in frequency or that contain doublets will maintain force output over longer periods of time than constant frequency stimulation in the thenar muscles of older healthy individuals and in chronic stroke survivors.

Hypothesis 1. An intermittent 20-40 Hz increasing frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of older healthy individuals.

Hypothesis 2. An intermittent doublet frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of older healthy individuals.

Hypothesis 3. An intermittent 20-40 Hz increasing frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of chronic stroke survivors.

Hypothesis 4. An intermittent doublet frequency train will maintain force output over a longer period of time than an intermittent constant 20 Hz frequency train in the thenar muscles of chronic stroke survivors.

Hypothesis 5: An intermittent 20-40 Hz increasing frequency train will maintain force output over a longer period of time in the thenar muscles of older healthy individuals than in chronic stroke survivors.

Hypothesis 6: An intermittent doublet frequency train will maintain force output over a longer period of time in the thenar muscles of older healthy individuals than in chronic stroke survivors.

Rationale: Lower overall force levels are typically seen in paralyzed muscle; variable stimulation patterns are needed to preserve force in denervated tissue.

**Study 3: The Impact of Electrical Stimulation Frequency on Rehabilitation of the Hand in Chronic Post-Stroke Individuals**

**Aim 1**: To determine if chronic stroke survivors who participate in a one-month rehabilitation program using high frequency stimulation (40 Hz) or low frequency stimulation (20 Hz) regimens will differ in voluntary strength and dexterity of the hemiplegic hand following training.

Hypothesis 1. Participants in the high frequency (40 Hz) stimulation program will gain greater pinch strength following training than participants in the low frequency (20 Hz) stimulation program.

Hypothesis 2. Participants in the high frequency (40 Hz) stimulation program will perform the Minnesota Dexterity Test faster following training than participants receiving the low frequency (20 Hz) stimulation program.

Hypothesis 3. Participants in the high frequency (40 Hz) stimulation program will err less in force accuracy tests following training than participants in the low frequency (20 Hz) stimulation program.

Hypothesis 4. Participants in the low frequency (20 Hz) electrical stimulation rehabilitation program will have greater endurance capacity in the thenar muscles of the hemiplegic hand following training than participants in the one-month high frequency (40 Hz) stimulation program.

Rationale: Higher frequencies will increase cortical and spinal excitability and additionally increase the probability of successful excitation-contraction coupling in muscle tissue. Muscles trained in extended endurance protocols using lower frequencies will perform better on endurance-type tests.

## SIGNIFICANCE OF STUDY

The specific electrical stimulation parameters that delay the onset of fatigue and maximize force output over time in the hand muscles of able-bodied individuals remain unknown. In addition, the electrical stimulation parameters that achieve these same goals in hemiplegic chronic post-stroke muscle have not been previously investigated. This study will provide novel information that may aid the development of clinical intervention programs and the design of neuroprosthetic devices, both of which will be critical factors in improving the quality of life for individuals paralyzed by stroke.

## DEFINITION OF TERMS

Operational definitions that will be used for the purposes of this study are as follows:

1. **Doublet** – two consecutive motor unit action potentials that occur with an interspike interval (ISI) or interpulse interval (IPI) of less than 20 ms (Simpson, 1969).

2. **Neuromuscular Electrical Stimulation (NMES)** – the use of electrical current to contract a muscle either through direct activation of the motor neurons in the peripheral nerve or indirectly through reflex recruitment (Baker et al, 2000).

3. **Endurance** - sustained motor output eliciting muscle force over a prolonged period (Thomas, 1997b)

4. **Fatigue** (muscle fatigue) – The state of muscle, following a period of intense or prolonged activity, characterized by a lessened capacity for work and reduced efficiency (Thomas, 1997b).

5. **Frequency** – number of pulses per second (pps) used to describe pulsed electrical currents; the rate of oscillation or alternation in cycles per second of an alternating current, expressed in hertz (Hz) (Thomas, 1997b).

6. **Functional Electrical Stimulation (FES)** – the use of electrical stimulation of the peripheral nervous system to activate muscle contractions to assist in functional activities, such as walking or upper extremity prehension (Baker et al, 2000).

7. **Hemiplegia** – Paralysis of one side of the body (Thomas, 1997b).

8. **M-Wave** – the compound muscle action potential and subsequent electrical response of the muscle when the motor nerve is stimulated (Allman et al, 2002).

## DELIMITATIONS AND LIMITATIONS

Some delimitations of the study existed due to 1) participants only being recruited from the Austin, Texas, area; therefore, generalizations cannot be made to other populations, 2) only those individuals whose native language is English were eligible for participation, 3) the level of education of individual participants was uncontrollable, thus varied greatly between participants, and 4) those individuals who participated did so as volunteers, which could have impacted study results.

Limitations of the study include the physical challenges faced by stroke survivors involved with this project. Fluctuations in physical abilities and stamina from one day to another are common in the post-stroke population and some visits were rescheduled in order to obtain optimal data. Submaximal electrical stimulation was used in the older and post-stroke participants for comfort and safety and these data are representative of muscle activity in a smaller number of fibers and may not provide information on whole muscle activity.

Although delimitations and limitations exist, efforts were made to optimize comfort and performance of the participants so as to ensure integrity of the data collected. Investigations such as these continue to contribute new and usable information to the overall body of knowledge that ultimately impacts scientific research as well as clinical practice. Also, information that provides insight into effective strategies for delaying the onset of fatigue in electrically stimulated muscles and for maximizing motor recovery in the hand following stroke is limited. This study can provide a scientific basis for promising interventions that may yield positive outcomes and fill the currently existing gaps in knowledge.

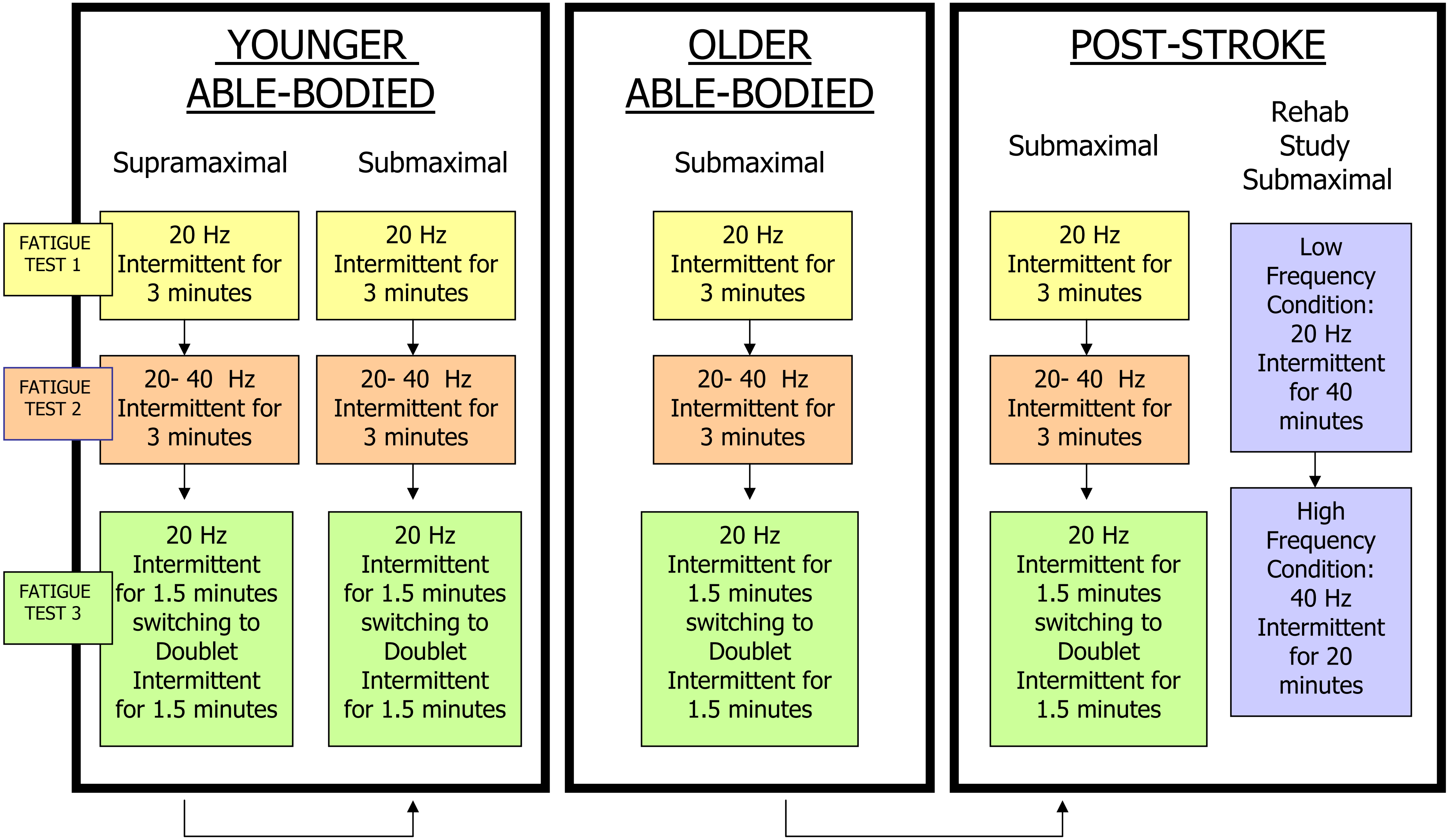


Figure I.1. Overview of studies conducted and statistical comparisons used. Downward arrows indicate within-group comparisons of fatigue tests (20 Hz vs. 20-40 Hz and 20 Hz vs. 20 Hz to doublet). Upward arrows indicate comparisons between participant groups (younger able-bodied maximal vs. younger able-bodied submaximal; older submaximal vs. post-stroke submaximal). For the stimulation studies, independent variables are the specific fatigue test pattern administered (20 Hz vs. 20-40 Hz or 20 Hz doublet), the level of stimulation (submaximal vs. maximal), subject group (young able-bodied; older able-bodied vs. post-stroke), and time (pre vs. post fatigue). Dependent measures will include force time integral (FTI) and M-wave amplitudes during fatigue tests, force values at 10, 20, 30, 40, and 50 Hz and maximal voluntary contraction force (MVC) pre and post fatigue tests. For the rehab study, dependent measures will be hand strength and dexterity.

# REVIEW OF LITERATURE

## MUSCLE FATIGUE

Muscle fatigue is defined as “any exercise-induced reduction in the ability to exert muscle force or power, regardless whether or not the task can be sustained.” (Gandevia, 2001). This may occur peripherally from processes at the muscle level, centrally, where decreasing cortical drive may be reduced (Gandevia, 2001), or at the spinal level from afferent III and IV input (Bigland-Ritchie, 1983).

Peripheral fatigue is thought to result from a number of changes in cellular processes at the muscle level. Whereas lactic acid accumulation was previously thought to be primarily responsible for muscular fatigue, more attention has been recently directed to the buildup of inorganic phosphates which can reduce overall contractile activity (Westerblad et al., 2002). These alterations in phosphate concentration have been suggested to contribute to the inhibition of sarcoplasmic reticulum calcium kinetics that eventually leads to reduction of force output (Steele et al., 2003). Mechanical and chemical alterations involving the t-tubule system of the sarcoplasmic reticulum and the calcium modulators, the ryanodine and dihydropyridine receptors, have also been described as playing a large role in the force decline associated with muscle fatigue (Gibson et al., 2001). Still other causes of fatigue and reduced work output have been attributed to myofibrillar tearing and breakdown of the myocellular framework, especially during performance of eccentric contractions (Green, 1997).

Failure to drive the motor neuron pool during muscle activation has been termed “central” fatigue. This results when cortical output slows during exercise and the task can no longer be continued with voluntary effort (for review, see Gandevia, 2001). Because fatigue can arise from several neural factors at many system levels, identification and separation of peripheral fatigue from central fatigue is often difficult.

At the level of the motor unit, changes have also been observed during the fatigue process. Marsden et al. (1983) proposed the "muscle wisdom" hypothesis which states that the slowing of motor unit firing rates typically seen during maximal voluntary contractions is an efficiency modulator, assisting in minimizing the overall fatigue response. Subsequent research demonstrated that this slowing is also a reflection of the whole muscle relaxation process (Bigland-Ritchie et al., 1983). Later, however, Garland et al. (1997) demonstrated that motor unit firing patterns did not slow in conjunction with a slowing of whole muscle relaxation time when observed in submaximal human contractions.

The condition of "low-frequency fatigue" (LFF) was first described in 1977 by Edwards et al., when they observed an inability of human muscle to be activated at lower frequencies (approximately 20 Hz) following fatigue. This condition persisted for up to 24 hours and did not occur when the muscle was stimulated with higher frequencies. This effect has been studied in animal models, where the repeated stimulation causes calcium to remain in the interstitial spaces of muscle cells for extended time periods, provoking an overall decrease of calcium from the sarcoplasmic reticulum (Chin, Balnave, & Allen, 1997). Because LFF typically occurs at frequencies within the 10-30 Hz range, the use of low frequencies of NMES have the potential to generate this effect. Binder-Macleod and Russ (1999) saw LFF in healthy quadriceps following brief intermittent stimulation trains. The amount of LFF present at 2 minutes post stimulation increased when measured again at 30 minutes post stimulation.

It appears that several multifaceted mechanisms may exist simultaneously and account for the fatigue effects seen in muscle. Indeed, the phenomenon of neuromuscular fatigue appears to be extremely complex and may be task-dependent, according to the method used to impart fatigue (voluntary effort or electrical), the intensity of contractions elicited, and the duration of the protocol (Enoka & Stuart, 1992).

#### ELECTRICAL STIMULATION AND MUSCLE FATIGUE

Voluntary movement is extremely efficient, firing many motor units throughout the muscle in an asynchronous pattern that conserves the overall energy expended and typically results in smooth, coordinated motion. NMES-elicited contractions, as compared to active voluntary contractions, are somewhat inefficient and cause motor units to fire in a synchronous manner. This can result in a rapid onset of fatigue. Therefore, electrically stimulated muscle is prone to fatigue more easily than a voluntarily contracted muscle.

Normal frequencies of human motor units during voluntary contractions are typically in the 5-12 Hz range when recruited, but can reach 40 Hz or higher during maximal contractions (Bigland-Ritchie, 1983). Higher frequencies experimentally administered in the 50 to 80Hz range have been required to produce maximal muscle force output; however, the extreme frequency caused a precipitous drop in force while a lower frequency of 20 Hz preserved the force output (Jones et al., 1979). Fuglevand and Keen (2003) used a 30 Hz constant stimulation pattern that sustained force more effectively than a decreasing 30 to 15 Hz pattern.

Strong evidence exists that higher frequencies of stimulation are needed to produce similar forces after a muscle becomes fatigued as compared to before. This rightward shift in the force-frequency relationship has been seen in single motor units (Thomas, Bigland-Ritchie, & Johansson, 1991; Fuglevand, Macefield, & Bigland-Ritchie, 1999) as well as in whole muscle (Edwards, Hill, Jones, & Merton, 1977;

Bergstrom & Hultman 1990; Binder-McLeod & McDermond 1992; Meyers, Nguyen, & Cafarelli, 2001; Russ, Vandenborne, & Binder-Macleod, 2002).

**STROKE**

Approximately every minute, on average, a person in the United States has a stroke. Almost 700,000 people suffer a first or recurrent stroke each year, and the overall stroke incidence rate has been shown to be highest in older age groups. More than 1.1 million Americans reported functional deficits and difficulty with activities of daily living due to residual dysfunction from stroke (American Heart Association, 2005). The CDC estimates that approximately $51.2 billion dollars was spent in 2005 as a result of direct and indirect costs related to stroke and over $60 billion dollars is projected to be spent in 2007.

Ischemic stroke creates anoxic conditions and post-infarct edema in the cortex that usually results in pronounced neuronal cell death. These conditions were once fatal but now many patients are able to survive due to advancements in surgical techniques and pharmacological procedures. From 1991 to 2005 the stroke rate rose by 7.7 percent and the death rate declined by 3.4 percent. About 6.8 million stroke survivors are alive today (American Heart Association, 2005). In a 2005 study of over 20,000 stroke survivors, 56% were diagnosed with left sided infarcts and 44% were diagnosed with right sided infarcts. The evidence suggested that right sided infarcts often go underdiagnosed due to the subtle nature of symptoms such as disturbances in judgment, thinking, and spatial awareness (Fink, 2005).

In addition to cognitive deficits, motor deficits are typically seen following stroke. The National Heart, Lung and Blood Institute's Framingham Heart Study found that 50 percent of stroke survivors had some one sided paralysis and 26 percent were dependent in activities of daily living (grooming, eating, bathing etc.). Thus, finding effective and efficient means to restore hand function lost due to stroke could have a significant impact on the quality of life for the stroke survivor and for society as a whole.

Hemiplegia following stroke renders the survivor unable to or inefficient in producing necessary forces in the muscles of the forearm and hand. Loss of function in corticospinal neurons that connect directly with spinal motor neurons impairs the ability of specific muscles to generate adequate force needed for hand movement (Farmer, Swash, Ingram, & Stephens, 1993). Debility of the upper extremity can persist for several weeks to months following stroke onset. Fine motor control and manual dexterity take longest to recover and can remain deficient for the rest of the lifespan.

Motor deficits in the extremities following stroke are the result of numerous factors including spasticity, soft tissue contractures or deformities, and weakness. However, the primary source of impaired motor function is the inability to generate and produce force from paralyzed muscle. This inability is related to the underlying neurophysiological changes that occur following stroke including decreased descending inputs (Terao et al., 1996) and altered motor unit activity such as decreased motor unit synchronization (Shepherd, 2001).

**PARALYZED MUSCLE**

Muscles paralyzed by stroke exhibit changes in chemical, neural, and mechanical properties. Because the incidence of stroke is highest in persons aged 55 years and older (American Heart Association, 2005), paralysis is usually imposed on muscle components that have undergone age-related physiological changes such as reduced calcium concentrations within the muscle and decreased sarcolemmal excitability (Carmeli, Coleman, & Reznick, 2002). Morphological changes such as loss of overall muscle mass, increased fat, increased density of connective tissue, and reduced tensile strength of tendons are also apparent (Carmeli, Patish, & Coleman, 2003). In addition, the number of viable motor units and muscle fibers is reduced resulting in loss of strength, and an increased reliance on slow twitch, fatigue resistant Type I fiber is usually observed (Allman & Rice, 2002).

Individual motor unit firing rates during the onset of a voluntary contraction as well as during maximal effort are typically reduced in the paralyzed individual and the incidence of doublets is more prevalent (Thomas et al. 2002). Individuals with a spastic motor recovery pattern show hyperactive stretch reflexes in antagonist muscles combined with weakness of agonists that can produce uncoordinated and often ineffective movement (Bourbonnais et al., 1989). In contrast, individuals with a flaccid motor recovery can experience physiological changes such as decreased muscle fiber size, density, capillarity, and bone density much like what is seen in muscles following non-use or during extended bed rest (Krasnoff & Painter, 1999). Finally, paralyzed muscle is notably weaker and has been shown to fatigue more rapidly than able-bodied muscle (Thomas, Griffin, Godfrey, Ribot-Ciscar, & Butler, 2003).

Paralyzed muscle produces lower forces and will fatigue more quickly than able-bodied muscle (Thomas et al., 2003). Thomas, Bigland-Ritchie, & Johansson (1991) showed that after fatigue, higher frequencies of stimulation are needed to produce pre-fatigue force levels in single motor units. To effectively delay the onset of fatigue within paralyzed muscles continues to be one of the most challenging research goals faced by scientists investigating this body of knowledge.

## AGED MUSCLE

Aging alters the morphology and fatigue properties of muscle. Sarcolemmal excitation, calcium handling, and excitation-contraction coupling mechanisms typically slow with age (for review, see Allman et al., 2002). Reduced calcium concentrations within the muscle have also been reported in aged muscle. (Carmeli et al, 2002). Neurological remodeling of motor units whereby fast motor neurons are lost and the orphaned fibers are often innervated by slower motor neurons is seen in advanced ages; this creates slower, less powerful muscle that fatigues more rapidly (Macaluso & DeVito, 2004; Connelly, Rice, Roos, & Vandervoort, 1999). The number of viable motor units and muscle fibers are also reduced in aged muscle, resulting in loss of strength and an increased reliance on slow twitch, fatigue-resistant Type I fibers (Allman & Rice, 2002). Greater fatigue resistance has been occasionally observed in older muscle when compared to young muscle (Rubinstein & Kamen, 2005; Lanza, Russ, & Ken-Braun, 2004) and fewer incidences of doublets in older muscle have also been reported (Christie & Kamen, 2006). The overall firing rate of motor units tends to be lower in older individuals as well (Semmler, 2003; Connelly et al., 1999). Additionally, the incidence of pathology involving neuronal changes (Drachman, 2006; Raz & Rodrigue, 2006), cardiovascular disease (Franklin, 2006), and musculoskeletal impairment (Narici & Maganaris, 2006; Blair & Carrington, 2006) increases with aging; all conditions which may present compounding factors influencing the response of older muscle to NMES.

## STROKE AND ELECTRICAL STIMULATION

Although exercise programs constitute an essential component of post-stroke rehabilitation, patients may not regain enough voluntary motor control in the upper extremity to fully and effectively perform exercise regimens. Newer and more technologically advanced methods of facilitating movement are necessary. In particular, the use of neuromuscular electrical stimulation (NMES) has been shown to have positive effects in facilitating active movement and enhancing motor function following neurological impairment. NMES is the application of a continuous current of electricity administered through a surface electrode at the nerve or motor point of a muscle to elicit a muscular contraction. The current is interrupted sporadically to allow for muscle relaxation, and the on/off durations, the intensity of the current, and the rate of current increase can be adjusted through a central unit controlled by the therapist (Pedretti, 1996). NMES has been shown to be helpful in strengthening muscles, restoring range of motion, and stimulating muscle contractions, especially in weak or denervated muscles that show limited active ability. Several studies have supported the effectiveness of NMES in increasing functional movement patterns in the upper extremity following stroke (Powell, Pandyan, Granat, Cameron, & Stott 1999; Peurala, Pitkanene, Sivenius, & Tarkka, 2002; Kimberley et al., 2004).

Use of electrical stimulation in rehabilitation following stroke can improve voluntary control of hand muscles (Popovic et al. 2002, Kimberley et al. 2004). Stimulation of peripheral nerves can result in both orthodromic and antidromic activation of motor and sensory neurons. EEG activity has also been found to occur in the sensorimotor and premotor areas of the cortex during NMES stimulation of the forearm muscles (Muller et al. 2003). Kimberley et al. (2004) used fMRI and found that activity in the somatosensory cortex increased after a take-home neuromuscular electrical stimulation system was used on the forearm extensor muscles. NMES is also effective for the treatment of hemispatial neglect following stroke (Eskes, Butler, McDonald, Harrison, & Phillips, 2003). Small portable electrical stimulation units are commercially available that enable a person to receive NMES treatment at their convenience. Many of these units can be programmed by the clinician whereby the patient can administer their own NMES treatment independently at home. Despite these technological advances, scientific evidence is sparse on the optimal stimulation parameters that should be used to restore maximal hand function in the post stroke individual.

**ELECTRICAL STIMULATION AND CELLULAR PROCESSSES**

The application of electrical stimulation to muscle imparts an external current that disrupts the homeostasis of the tissues beneath the electrodes. Cellular depolarization occurs when the current passes through the electrodes into the skin layers beneath creating a negative field that attracts sodium ions and lowers the threshold for an action potential to occur (Baker, Wederich, Mc Neal, Newsam, & Waters, 2000). The electrical current encounters impedance in the way of skin, fatty tissue, connective tissue and bone to reach the muscle or nerve and therefore an increase of current intensity may be required to achieve tetany. The force output obtained is ultimately modulated by intensity, which determines the amount of recruitment of muscle fibers, and frequency, which will impact the rate at which motor neurons fire; frequencies of 25 Hz typically have been shown to achieve a smooth contraction (Mourselas & Granat, 1998). See Figure I.2 for an example of force output with 20 Hz intermittent stimulation.

Because electrical stimulation targets fibers of least resistance, larger, faster motor units are activated initially and synchronously, causing an excessive amount of fatigue. Higher frequencies of stimulation are thus required to activate fatigued muscle to produce force similar to pre-fatigue levels (Thomas et al., 1991; Fuglevand et al., 1999). Stimulation trains that vary in frequency or apply closely spaced pulses have been shown to consistently enhance force more effectively when compared to constant frequency trains (Maladen et al., 2007; Scott et al., 2007; Allman et al., 2004). Variable trains have also been shown to produce a faster rise time in force, thought to be a result of a rapid increase of calcium from the sarcoplasmic reticulum (Slade et al., 2003). Additionally, higher frequency pulses have the potential to create a sudden increase in tissue stiffness by tightening the series elastic element, which could account for the increase in force enhancement (Binder-Macleod & Lee, 1996). Muscle that has fatigued tends to become slack and compliant, and would tend to respond favorably to the increased tension (Vigreux, et al., 1980).

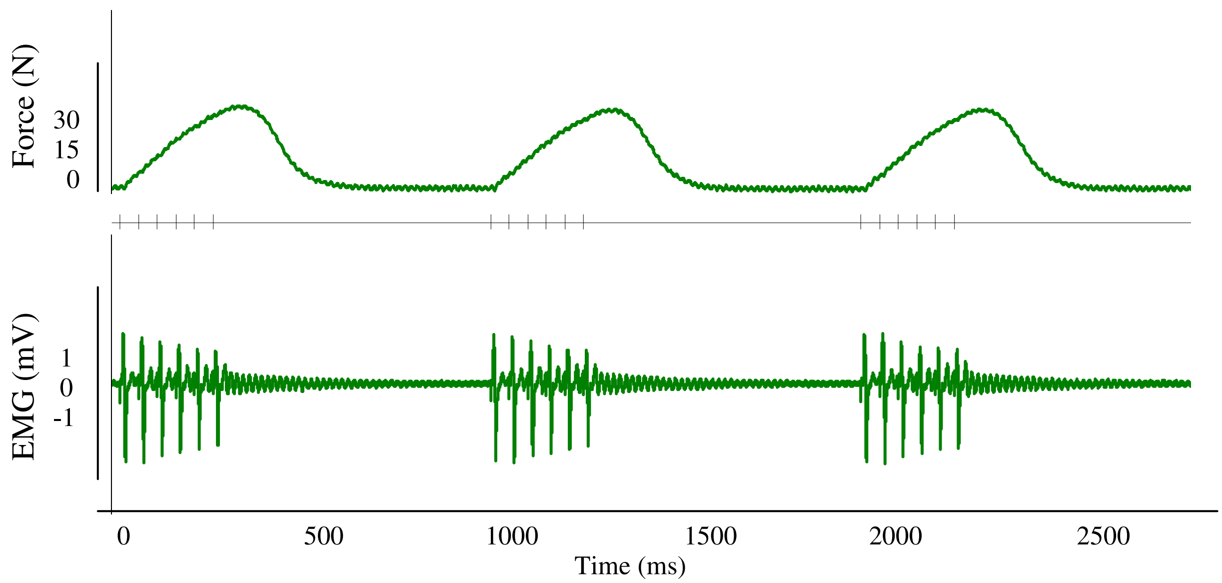


Figure I. 2. Raw data from an intermittent 20 Hz stimulation. Top trace, resultant force, middle trace, stimulation pulses, bottom trace, EMG showing M-waves.

**REFERENCES**


Allman, B. L., & Rice, C. L. (2002). Neuromuscular fatigue and aging: central and peripheral factors. *Muscle & Nerve, 25*, 785-796.

American Heart Association. (2005). *Heart disease and stroke statistics – 2004 update*. Dallas, TX: www.americanheart.org.

Baker, L. L., Wederich, C. L., McNeal, D. R., Newsam, C., & Waters, R. L. (2000). *Neuromuscular electrical stimulation,* (4th Ed.). Los Amigos Research & Education Institute: Downey, CA.

Bevan L., Laouris Y., Reinking, R. M., & Stuart, D. G.(1992). The effect of the stimulation pattern on the fatigue of single motor units in adult cats. *Journal of Physiology, 449,* 85-108.

Bigland-Ritchie, B. R., Johansson, R., Lipipold, O. C. J., & Woods, J. J. (1983). Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *Journal of Neurophysiology, 50,* 313-324.

Bigland-Ritchie, B. Zijdewind, I., & Thomas, C. K. (2000). Muscle fatigue induced by stimulation with and without doublets. *Muscle & Nerve, 23,* 1348-1355.

Binder-Macleod, S. A., Lee, S. C., Russ, D. W., & Kucharski, L. J. (1998). Effects of activation pattern on human skeletal muscle fatigue. *Muscle & Nerve, 21,* 1145-1152.

Binder-Macleod, S. A., & Scott, W. B. (2001). Comparison of fatigue produced by various electrical stimulation trains. *Acta Physiologica Scandinavia, 172,* 195-203.

Brunt, D., Vander Linden, D. W., & Behrman, A. L. (1995). The relation between limb loading and control parameters of gait initiation in persons with stroke. *Archives of Physical Medicine & Rehabilitation, 76* (7), 627-634.

Brust, J. C. M. (2000). Circulation of the brain. In Kandel, Schwartz, & Jessell (Eds.), *Principles of Neural Science* (pp.1302-1316).

Bourbonnais, D. & Vanden Noven, S. (1989). Weakness in patients with hemiparesis. *American Journal of Occupational Therapy, 43* (5), 313-319.

Carmeli, Patish, & Coleman. (2003). The aging hand. *Gerontology and Biological Science and Medical Science*, 58, 146-52.

Chae, J., Bethoux, F., Bohine, T., Dobos, L., Davis, T., & Friedl, A. (1998). Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. *Stroke, 29* (5), 975-979.

Chae, J., & Yu, D. (2002). Neuromuscular electrical stimulation for motor restoration in hemiparesis. Topics in Stroke Rehabilitation, 8 (4), 24-39.

Chin, E. R., Balnave, C. D., & Allen, D. G. (1997). Role of intracellular calcium and metabolites in low-frequency fatigue of mouse skeletal muscle. American Journal of Physiology and Cellular Physiology, 272, C550-C559.

Cooper, S. & Eccles, J. C. (1930). The isometric responses of mammalian muscles. Journal of Physiology, 69, 377-385.

Daly, J. J., & Ruff, R. L. (2000). Electrically induced recovery of gait components for older patients with chronic stroke. *American Journal of Physical Medicine and Rehabilitation, 79*(4), 349-360.

deKroon, J. R., Ijzerman, M. J., Chae, J., Lankhorst, G. J., & Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *Journal of Rehabilitation Medicine, 37,* 65-74.

Duchateau, J. & Hainaut, K. (1986). Nonlinear summation of contractions in striated muscle. I. Twitch potentiation in human muscle**.** *Journal of Muscle Research & Cell Motility, 7*(1), 11-17.

Eberstein, A., & Eberstein, S. (1996). Electrical stimulation of denervated muscle: is it worthwhile? *Medical Science of Sport and Exercise, 28* (12), 1463-1469.

Edwards, R. H., Hill, D. K., Jones, D. A., & Merton, P. A. (1977). Fatigue of long duration in human skeletal muscle after exercise. *Journal of Physiology (London), 272,* 769-778.

Enoka, R. M., & Stuart, D. G. (1992). Neurobiology of muscle fatigue. *Journal of Applied Physiology, 72,* 1631-1648.

Eskes, G. A., Butler, B., McDonald, A. Harrison, E. R. and Phillips, S. J. (2003). Limb activation effects in hemispatial neglect. *Archives of Physical Medicine and Rehabilitation, 84*, 323-328.

Farmer, S. F., Swash, M., Ingram, D. A., & Stephens, J. A. (1993). Changes in motor unit synchronization following central nervous lesions in man. *Journal of Physiology, 463*, 83-105

Fink, J. N. (2005). Underdiagnosis of right-brain stroke. *The Lancet, 366* (9483), 349-351.

Fuglevand, A. J., Keen, D. A. (2003). Reevaluation of muscle wisdom in the human adductor pollicis using physiological rates of stimulation. *Journal of Physiology, 549,* 865-75.

Gandevia, S. C. (1991). Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews, 81,* 1725-1789.

Garland, S. J., Griffin, L., Ivanova, T. (1997). Motor unit discharge rate is not associated with muscle relaxation time in sustained submaximal contractions in humans. Neuroscience Letters, 239, 25-28.

Gibson, A. S., Lambert, M. I., & Noakes, T. D. (2001). Neural control of force output during maximal and submaximal exercise. *Sports Medicine, 31* (9), 637-650.

Green, H. J. (1997). Mechanisms of muscle fatigue in intense exercise. *Journal of Sports Science, 15* (3), 247-256.

Griffin, L., & Cafarelli, E. (2006). Transcranial stimulation during resistance training of the tibialis anterior muscle. *Journal of Electromyography & Kinesiology,* (in press).

Griffin, L., & Cafarelli, E. (2005). Resistance training: cortical, spinal, and motor unit adaptations. *Canadian Journal of Applied Physiology, 30* (3), 328-340.

Griffin, L., Garland, S. J. and Ivanova, T. (2000). Role of limb movement in the modulation of motor unit discharge during fatiguing contractions. *Experimental Brain Research, 130*, 392-400.

Griffin, L. & Jun, B. G. (2004). Considerations of stimulation parameters within the physiological range.

Jones, D. A., Bigland-Ritchie, B. R., & Edwards, R. H. T. (1979). Excitation frequency and muscle fatigue: Mechanical responses during voluntary and stimulated contractions. *Experimental Neurology, 64,* 401-413.

Karu, Z. Z., Durfee, W. K., & Barzilai, A. M. (1995). Reducing muscle fatigue in FES applications by stimulating with N-let pulse trains. *IEEE Transcripts of Biomedical Engineering, 42*(8), 809-817.

Kebaetse, M. B., & Binder-Macleod, S. A. (2004). Strategies that improve human skeletal muscle performance during repetitive, non-isometric contractions. *Pflugers Archives, 448*(5), 525-32.

Kebaetse, M. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Strategies that improve paralyzed human quadriceps femoris muscle performance during repetitive, non-isometric contractions. *Archives of Physical Medicine and Rehabilitation, 86* (11), 2157-2164.

Keen, D. A., Yue, G. H., & Enoka, R. M. (1994). Training-related enhancement in the control of motor output in elderly humans. *Journal of Applied Physiology, 77,* 2648-2658.

Kimberley, T. J., Lewis, S. M., Auerbach, E. J., Dorsey L. L., Lojovich, J. M., & Carey, J.R. (2004). Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Experimental Brain Research, 154*(4):450-60.

Kluding, P., & Billinger, S. A. (2005). Exercise-induced changes of the upper extremity in chronic stroke survivors. *Topics in Stroke Rehabilitation, 12* (1), 58-68.

Krasnoff, J. & Painter, P. (1999). The physiological consequences of bed rest and inactivity. *Advances in renal replacement therapy, 6* (2), 124-132.

Laidlaw, D. H., Bilodeau, M., & Enoka, R. M. (2000). Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle & Nerve, 23,* 600-612.

Liberson, W. T., Holmquest, H. J., Scott, D., & Dow, M. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of gait of hemiplegia patients. *Archives of Physical Medicine & Rehabilitation, 42*, 101-105.

Macefield, V. G., Fuglevand, A. J., & Bigland-Ritchie, B. (1996). Contractile properties of single motor units in human toe extensors assessed by intraneural motor axon stimulation. *Journal of Neurophysiology, 75*(6), 2509-2519.

MacIntosh, B. R., & Willis, J. C. (2000). Force-frequency relationship and potentiation in mammalian skeletal muscle. *Journal of Applied Physiology, 88*(6), 2088-2096.

Marsden, C. D., Meadows, J. C., Merton, P. A. (1983). Muscular wisdom" that minimizes fatigue during prolonged effort in man: peak rates of motoneuron discharge and slowing of discharge during fatigue. *Advances in Neurology, 39*, 169-211.

Pedretti, L. W. (1996). *Occupational therapy for physical dysfunction*. New York: Mosby.

Peurala, S. H., Pitkanen, K., Sivenius, J., & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clinical Rehabilitation,16*, 709-716.

Pitcher, J. B., Ridding, M. C., Miles, T. S. (2003). Frequency dependent, bi-directional plasticity in motor cortex of human adults. *Clinical Neurophysiology, 114,* 1265-1271.

Popovic, M.B., Popovic, D.B., Sinkjaer,T., Stefanovic, A., & Schwirtlich, L. (2002). Restitution of reaching and grasping promoted by functional electrical therapy. *Artificial Organs, 26* (3), 271-275.

Powell, J., Pandyan, D., & Granat, M. (1999). Electrical stimulation of wrist extensors in post-stroke hemiplegia. *Stroke*, 30, 1384-1389.

Ratkevicius, A., & Quistorff, B. (2002). Metabolic costs of force generation for constant-frequency and catchlike-inducing electrical stimulation in human tibialis anterior muscle. *Muscle & Nerve, 25*(3), 419-426.

Simpson, J. A. (1969). Terminology of electromyography. *Electroencephalography and Clinical Neurophysiology, 26,* 224-226.

Spriett, L. L., Soderlund, K., & Hultman, E. (1988). Energy cost and metabolic regulation during intermittent and continuous titanic contractions in human skeletal muscle. *Canadian Journal of Physiology & Pharmacology, 66* (2), 134-139.

Steele, D. S., & Duke, A. M. (2003). Metabolic factors contributing to altered Ca2+ regulation in skeletal muscle fatigue. *Acta Physiologica Scandinavia, 179* (1), 39-48.

Terao, S., Takahashi, M., Li, M., Hashizume, Y., Ikeda, H., Mitsuma, T., & Sobue, G. (1996). Selective loss of small myelinated fibers in the lateral corticospinal tract due to midbrain infarction. *Neurology, 47*(2), 588-591.

Thomas, C. K. (1997a). Contractile properties of human thenar muscles paralyzed by spinal cord injury. *Muscle & Nerve*, *20* (7), 788-799.

Thomas, C. K., Bigland-Ritchie, B., Johansson, R. S. (1991) Force-frequency relationships of human thenar motor units. *Journal of Neurophysiology, 65*, 1509-1516.

Thomas, C. K., Butler, J. E., & Zijdewind, I. (2002). Patterns of pathological firing in human motor units. In S. C. Gandevia, U. Proske, and D. G. Stuart (Eds), *Advances in experimental medicine and biology* (pp. 237-244). New York: Kluwer Academic.

Thomas, C. K., Griffin, L., Godfrey, S., Ribot-Cisar, E., & Butler, J. E. (2003). Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *Journal of Neurophysiology, 89*, 202-204.

Thomas, C. L. (Ed.). (1997b). *Taber's cyclopedic medical dictionary* (18th ed.). Philadelphia: F. A. Davis.

Van Cutsem, M. V., Duchateau, J., & Hainut, K. (1998). Changes in single motor unit behaviour contribute to the increase in contraction speed after dynamic training in humans. *Journal of Physiology, 513,* 295-305.

Van Lunteren, F., & Sankey, C. B. (2000). Catchlike property of rat diaphragm: subsequent train frequency effects in variable-train stimulation**.** *Journal of Applied Physiology, 88*(2), 586-598.

Westerblad, H., Allen, D. G., & Lannergren, J. (2002). Muscle fatigue: Lactic acid or inorganic phosphate the major cause? *News In Physiological Science, 17,* 17-21.

Yan, T., & Hui-Chan, C. W. (2005). Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial. *Stroke, 36* (1), 932-933.

Yu, D. T., Chae, J., Walker, M. E., Kirstens, A., Elovic, E. P., Flanaga, S. R., Harvey, R. L., Zorowitz, R. D., Frost, F. S., Grill, J. H., Feldstein, M. & Fang, Z. P. (2004). Intramuscular neuromuscular electric stimulation for poststroke shoulder pain: a multicenter randomized clinical trial. *Archives of Physical Medicine and Rehabilitation, 85* (5), 695-704.

Zijdewind, I., & Thomas, C. K. (2003). Motor unit firing during and after voluntary contractions of human thenar muscles weakened by spinal cord injury. *Journal of Neurophysiology, 89,* 2065-2071

# Chapter 1: Variable Neuromuscular Electrical Stimulation: The Effect of Submaximal and Maximal Intensities

## ABSTRACT

Neuromuscular electrical stimulation (NMES) is effective for recovery of motor function following injury or pathology, however, NMES can impart rapid fatigue and the specific parameters of stimulation that maximize force output and delay the onset of fatigue remain unclear. Variable stimulation patterns have been previously examined, and in most cases, are administered using submaximal stimulation levels that target a limited number of muscle fibers. Responses obtained using this method may not be representative of motor behavior of the whole muscle. To determine if stimulation intensity impacted the fatigue response, we investigated three different variable stimulation patterns and compared the effects at submaximal as well as supramaximal intensities. Ten young healthy individuals were tested with three 3-minute intermittent stimulation patterns applied to the thenar muscle at both intensities: 1) a 20 Hz pattern, 2) a pattern of 90s at 20 Hz followed by 90s of a gradual increase from 20 Hz to 40 Hz; and 3) a pattern of 90s of 20 Hz followed by 90s of doublets. Significant differences were found overall between the submaximal and supramaximal stimulation intensity conditions. At submaximal intensities, the doublet pattern showed a significantly higher FTI (1.40 ± 0.02 kN•s vs. 1.05 ± 0.01 kN•s for 20 Hz and 1.17 ± 0.01 kN•s for 20-40 Hz), higher average forces (7.89 ± 2.79 N vs. 5.99 ± 0.87 N for 20 Hz and 6.66 ± 0.93 N for 20-40 Hz) and a higher peak force overall (11.02 ± 0.88 N vs. 8.30 ± 0.27 N for 20 Hz and 9.35 ± 0.25 N for 20-40 Hz). At supramaximal intensities, the doublet pattern

showed the lowest FTI, 1.54 ± 0.01 kN•s vs. 1.62 ± 0.01 kN•s for the 20 Hz and 1.69 ±0.01 kN•s for the 20-40 Hz pattern. Variable stimulation patterns administered to the thenar muscle of young healthy individuals showed significantly different results at submaximal and supramaximal intensities. Consideration of parameters and intensities should be given when investigating the motor benefits of NMES and when using this modality in clinical settings.

## INTRODUCTION

Neuromuscular electrical stimulation (NMES) has proven to be a useful modality in facilitating movement in muscles affected by neurological impairment and paralysis. However, the use of NMES imparts rapid fatigue to already weakened and denervated muscle thereby limiting extended force production and the ability to successfully participate in strengthening and rehabilitative regimens. Several studies have manipulated the characteristics of NMES to determine how to maximize force output and delay the onset of fatigue; however, the majority of these investigations have used submaximal stimulation protocols that may not reflect whole muscle behavior (Table 1.1). Additionally, the use of varying frequencies and pulse patterns has shown to be effective in extending force output in several instances during submaximal stimulation (Gregory, Dixon, & Bickel, 2007; Kesar, Chou, & Binder-Macleod, 2007; Scott, Lee, Johnston, Binkley, & Binder-Macleod, 2007), but whether the same results are obtained during supramaximal stimulation is not yet known.

A submaximal stimulation level typically only activates a portion of the muscle fibers being stimulated; a supramaximal stimulation level recruits the maximum number of motor units during the contraction. Godfrey, Butler, Griffin, and Thomas (2002) compared submaximal and supramaximal median nerve stimulation of spinal-injury paralyzed individuals. They found that submaximal intensities showed less relative force loss, force-time integral decline, and slowing of half-relaxation time following fatigue than did stimulation at supramaximal intensities. Furthermore, they reiterated that, because a maximum number of motor axons were being stimulated, more variables were controlled during supramaximal stimulation; submaximal stimulation results were inconsistent and may not have activated the same fibers on repeated sessions. Non-fatigued tibialis anterior muscles likewise showed unreliable forces when stimulated at

| Authors & Year of Publication | Muscle & Population Studied | Type of Contraction | Intensity of Stimulation | Stimulation Trains Used | Outcome |
|---|---|---|---|---|---|
| Gregory, Dixon, & Bickel, 2007 | Healthy quadriceps | Isometric | S | VFT<br>VPW | Using lower frequencies and modifying pulse durations may predictably control torque output and reduce fatigue |
| Kesar, Chou, & Binder-Macleod, 2007 | Healthy quadriceps | Isometric | S | CFT<br>VFT<br>CPW<br>VPW | Frequency modulation showed better peak forces and FTIs than pulse-width modulation with equal fatigue |
| Maladen, Perumal, Wexler, & Binder-Macleod, 2007 | Healthy quadriceps | Non-isometric | S | CFT<br>VFT<br>DIT<br>DFT | VFT produced greater muscle excursion than CFT |
| Scott, Lee, Johnston, Binkley, & Binder-Macleod, 2007 | SCI Paralyzed quadriceps | Isometric | S | CFT<br>VFT<br>DFT | VFT and DFT peak forces greater than CFT; DFT FTIs greater in non-fatigued muscle, but no difference in trains with fatigued muscle |
| Baldwin, Klakowicz, & Collins, 2006 | Healthy triceps surae & wrist flexors | Isometric | S | CFT | In triceps, direct muscle stimulation more effective than tibial nerve stimulation for contraction amplitude and consistency; two stimulation types similar in wrist flexors. |
| Griffin, Jun, Covington, & Doucet, 2006 | Healthy thenar | Isometric | M | CFT<br>VFT | No difference in FTI of CFT and trains that increase (20-40Hz) or decrease (40-20Hz) |
| Gorgey, Mahoney, Kendall, & Dudley, 2006 | Healthy quadriceps | Isometric | S | VFT<br>VPW<br>VA | Shorter pulse widths and lower frequencies decrease specific tension, while altering amplitude had no effect |
| Kesar & Binder-Macleod, 2006 | Healthy quadriceps | Isometric | S | VFT<br>VPW | Stimulation trains using lower frequencies with longer pulse widths produce lowest declines in force and less fatigue. |
| Shields, Dudley-Javoroski, & Cole, 2006 | Paralyzed soleus | Isometric | M | CFT<br>VFT<br>DIT | Feedback-controlled stimulation using higher frequencies more effective in enhancing torque output |
| Kebaetse, Lee, Johnston, & Binder-Macleod, 2005 | Paralyzed quadriceps | Non-isometric | S | CFT<br>DFT | Starting with lower frequencies and switching to higher frequencies as muscle fatigued produced more knee extension repetitions |
| Scott, Lee, Johnston, & Binder-Macleod, 2005 | Paralyzed quadriceps | Isometric | S | CFT<br>DFT | When DFTs followed CFTs, target isometric force was reached more often than when CFTs used alone |
| Allman, Cheng, & Rice, 2004 | Healthy young and older quadriceps | Isometric | S | CFT<br>CIT | Peak force and LFF not affected by age; greater FTI seen in older; CIT produced greater force in fatigued muscle; repetitive CIT induces greater fatigue |
| Allman & Rice, 2004 | Healthy young and older quadriceps | Isometric | S | CFT<br>NFT | Trains using frequencies adjusted for age-related shift in force-frequency curve (NFT) showed greater fatigue resistance in older |

| | | | | | |
|---|---|---|---|---|---|
| Kebaetse & Binder-Macleod, 2004 | Healthy quadriceps | Non-isometric | S | VFT | Low-frequency trains followed by high-frequency trains produced the best performance of repetitive knee extension |
| Scott Bickel, Slade, Van Hiel, Warren, & Dudley, 2004 | Healthy and SCI paralyzed quadriceps | Isometric | S | CFT<br>VFT | VFT enhanced TTI in healthy; less pronounced effect in paralyzed |
| Bickel, Slade, & Warren, 2003 | Healthy quadriceps and tibialis anterior | Isometric | S | CFT<br>VFT | VFT enhanced torque similarly in both muscles |
| Scott & Binder-Macleod, 2003 | Healthy quadriceps | Isometric | S | CFT<br>DFT | Combining CFT and DFT may offset fatigue |
| Thomas, Griffin, Godfrey, Ribot-Ciscar & Butler, 2003 | SCI paralyzed & healthy Thenar | Non-isometric | S | CFT (20 & 40Hz)<br>VFT (20 & 40Hz) | Force loss present in both groups, but less in healthy participants; frequency, pulse pattern, & pulse number had minimal effect on fatigue |
| Slade, Bickel, Warren, & Dudley, 2003 | Healthy quadriceps | Isometric | S | CFT<br>VFT | VFT enhanced torque in fatigued muscle better than CFT and low (25%MVC) and high (50%MVC) intensities |
| Griffin, Godfrey, & Thomas, 2002 | SCI paralyzed & healthy thenar | Isometric | M | DIT | FTI greatest in both muscle types when trains are initiated by a doublet separated by 5-15ms followed by longer doublet intervals; paralysis does not impact optimal pulse pattern effect |
| Kebaetse, Turner, & Binder-Macleod, 2002 | Healthy quadriceps | Non-isometric | S | CFT<br>VFT<br>DFT | No pattern optimal for all subjects; higher frequencies of CFT, VFT and DFT better in reaching knee extension targets |
| Ratkevicius & Quistorff, 2002 | Healthy tibialis anterior | Isometric | M | CFT<br>CIT | CIT more effective in maintaining FTI and generated force more quickly than CFT; ATP use during both trains similar |
| Russ, Vandenborne, & Binder-Macleod, 2002 | Healthy quadriceps | Isometric | S | CFT<br>VPW | Trains of varying frequencies and pulse widths all produced greater fatigue at low frequencies; validates presence of LFF using different parameters |
| Allman & Rice, 2001 | Healthy young and old biceps | Isometric | M | CFT | Recovery of fatigue during voluntary or evoked contractions is not different in young and old |
| Binder-Macleod & Scott, 2001 | Healthy quadriceps | Isometric | S | CFT<br>DIT<br>DFT | DIT and DFT produced greater FTI and peak forces than CFT in fatigued muscle. Optimization of force may involve switching patterns. |
| Kebaetse, Lee, & Binder-Macleod, 2001 | Healthy quadriceps | Non-isometric | S | CFT<br>VFT<br>DFT | DFT better for reaching knee extension targets |
| Laufer, Ries, Leininger, & Alon, 2001 | Healthy quadriceps | Isometric | S | CFT | Examined effect of different waveforms while keeping frequency, pulse width, duration constant. Mon- and bi-phasic waveforms produced greater torque and less fatigue than polyphasic; stronger contractions seen in male subjects |
| Bigland-Ritchie, Zijdewind, & Thomas 2000 | Healthy thenar | Isometric | M | CFT<br>DIT | Trains that contained doublets showed less force and FTI decline as well as less increases in HRTcompared to 40Hz |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | bursts |
| Lee & Binder-Macleod, 2000 | Healthy quadriceps | Non-Isometric | S | CFT CIT | In fatigued muscle, CIT produced greater overall performance than CFT |
| Lee, Becker, & Binder-Macleod, 2000 | Healthy quadriceps | Non-isometric with load | S | CFT CIT | CIT augmented force at highest loads |
| Binder-Macleod & Russ, 1999 | Healthy quadriceps | Isometric | S | CFT VFT | Greater LFF and highest FTI in VFT and low frequency (9 & 14 Hz) trains |
| Russ & Binder-Macleod, 1999 | Healthy quadriceps | Isometric | S | CFT VFT | VFT allow muscle to generate more force during fatigue and may offset the long-term effects of LFF |
| Thomas, Johansson, & Bigland-Ritchie, 1999 | Healthy thenar | Isometric | M | DIT | Trains initiated by doublets with a 5-10ms IPI produced best FTI |
| Binder-Macleod, Lee, Russ, & Kucharski, 1998 | Healthy quadriceps | Isometric | S | CFT VFT | VFT produced greater FTI; higher FTI also seen when fatigued with CFT |
| Mourselas & Granat, 1998 | Healthy and SCI paralyzed quadriceps | Isometric | S | CFT VFT | VFT produced enhanced muscle output when doublets with IPI of 5 ms used; effect decreases with higher stimulation intensities |
| Binder-Macleod, Lee, & Baadte, 1997 | Healthy quadriceps | Isometric | S | CFT VFT | VFT were effective only in fatigued muscle; greater FTI and rates of rise in force during VFT |
| Binder-Macleod & Lee, 1996 | Healthy quadriceps | Isovelocity | S | CFT CIT | CITs showed greater force and rate of rise than CFTs in fresh and fatigued muscle; CITs less effective during eccentric contractions |
| Leiber & Kelly, 1996 | Healthy quadriceps | Isometric | S | CFT | Variable duty cycles studied; Higher frequencies and greater duty cycles showed greater torque decreases; greatest average torque in a 50Hz/50% duty cycle; fewer longer duration contractions maximizes muscle tension |
| Karu, Durfee, & Barzilai, 1995 | Healthy and SCI paralyzed quadriceps | Isometric | S | VFT | Doublets with an IPI of about 5 ms produced the maximum torque-time integral per pulse; doublets better than single pulses to enhance force |
| Miller & Thepaut-Mathieu, 1993 | Healthy quadriceps | Isometric | S | CFT | Resultant electrically-evoked torque a important determinant of FES efficacy; no correlation between current level and strength changes after FES training |
| Binder-Macleod & Barker, 1991 | Healthy quadriceps | Isometric | S | CFT VFT | VFT shows greater forces after repetitive contractions; VFTs show advantage over CFT for FES |
| Binder-Macleod & Guerin, 1990 | Healthy quadriceps | Isometric | S | CFT VFT | Reduction of frequency during a fatiguing contraction may decrease rate of force fatigue. VFT protocol may be more effective than CFT. |

Table 1.1 Relevant human neuromuscular electrical stimulation studies conducted using variable stimulation patterns at submaximal (S) or maximal/supramaximal (M) intensity levels. Abbreviations: VFT-variable frequency train; VPW- variable pulse width; CFT-constant frequency train; CPW- constant pulse width; DIT-doublet initiated train; DFT-doublet frequency train; CIT-catchlike inducing train; VA-variable amplitude; NFT-normalized frequency train; FTI-force time integral; TTI-torque time integral; LFF-low frequency fatigue; IPI-interpulse interval; HRT-half relaxation time.

submaximal intensities. This was especially prevalent when contractions at less than a 10% MVC were attempted (Hanchard, Williamson, Caley, and Cooper, 1998). Therefore, the validity of using submaximal stimulation intensities of NMES to extrapolate the contractile properties of whole muscle remains questionable and requires further investigation.

Because effective muscle contraction is a vital component of any strengthening or retraining program, selecting a frequency that is adequate to achieve a functional level of tetany without excess neuromuscular fatigue is paramount. Several investigations have conclusively determined that stimulation administered at constant frequencies is not as effective in maximizing force output when compared to variable frequency stimulation patterns. Maladen, Perumal, Wexler, & Binder-Macleod (2007) compared constant, variable, and doublet stimulation trains administered to the human quadriceps muscle at several frequencies and showed that trains that incorporated variable inter-pulse intervals (IPI) and included doublets were more successful in obtaining specified muscle excursion targets than constant frequency trains. Likewise, when an arc of 50° active knee extension was set as a target task, doublet frequency stimulation trains and variable frequency trains were consistently more effective in reaching the targeted excursion than constant frequency trains (Kebaetse, Lee, & Binder-Macleod, 2001). In addition, a combination train that began with constant frequency pulses then switched to doublet frequency pulses when a targeted quadriceps isometric force was no longer produced was more effective in increasing overall force output than when constant-frequency-only or doublet-frequency-only stimulation trains were used (Scott & Binder-Macleod, 2003). When constant frequency stimulation and variable stimulation protocols were compared in the quadriceps of young and old men, the variable frequency trains produced greater force than the constant frequency trains after the muscle was fatigued (Allman, Cheng, & Rice, 2004). Variable frequency trains have also been effective in extending force over time in spinal-injury (SI) paralyzed muscle. Scott Bickel, Slade, Van Hiel, Warren, & Dudley (2004) found that torque-time integral was greater when variable frequency patterns were used on fatigued SI-paralyzed quadriceps than when constant frequency trains were used.

In addition, strong evidence exists that higher frequencies are needed to produce similar forces after a muscle becomes fatigued as compared to before. This rightward shift in the force-frequency relationship has been seen in single motor units (Thomas, Bigland-Ritchie, & Johansson, 1991; Fuglevand, Macefield, & Bigland-Ritchie, 1999) as well as in whole muscle (Edwards, Hill, Jones, & Merton, 1977; Bergstrom & Hultman 1990; Binder-McLeod & McDermond 1992; Meyers, Nguyen, & Cafarelli, 2001; Russ, Vandenborne, & Binder-Macleod, 2002). Lower frequencies of stimulation can also impart "low frequency fatigue," a condition where more force is lost at lower frequencies as compared to higher frequencies when muscle is stimulated after being fatigued (Edwards et al., 1977).

More complex stimulation characteristics, such as the incorporation of trains that change pulse patterns, may also enhance force production. Electrical stimulation with doublets has recently shown potential in optimizing force output. Kebaetse and Binder-Macleod (2004) found that during submaximal stimulation of the human quadriceps muscle of able-bodied younger adults, a constant frequency train that switched to a higher frequency train containing doublets produced greater force output than constant low (20 Hz) and high (40 Hz) frequency trains. Thus it is possible that a train that incorporates doublets will reduce the rate of fatigue and prolong force output over time. Several other studies have investigated the use of doublets during fatiguing contractions. Most tested brief trains of stimulation and found that the trains with doublets produce significantly more force than trains without doublets (Duchateau & Hainaut 1986; Macefield, Fuglevand, & Bigland-Ritchie, 1996; Van Lunteren & Sankey 2000; Griffin, Godfrey, & Thomas, 2002) and that the force enhancement with doublets is even greater following fatigue (Karu, Durfee, & Barzilai. 1995; Ratkevicius and Quistorff, 2002) and in paralyzed versus non paralyzed muscle (Griffin, Godfrey, & Thomas, 2002). Doublets have also produced force enhancement in more extended protocols of repetitive brief trains (Binder-Macleod & Scott 2001; Bevan et al. 1992; Bigland-Ritchie, Zijdewind, & Thomas, 2000). Thomas, Griffin, Godfrey, Ribot-Ciscar, and Butler, (2003) found that the fatigue response using this pattern was no different when compared to constant patterns, but Binder-Macleod, Lee, Russ, and Kucharski (1998) found greater force loss after doublet trains than when constant frequency trains were used.

We also chose to examine the effects of "low-frequency fatigue" in this investigation. Low-frequency fatigue (LFF) was first described by Edwards, Hill, Jones, and Merton (1977) and has been frequently observed by others (Russ & Vandenborne, 2002; Westerblad & Allen, 2002). LFF is a condition in which significant force loss is seen during stimulation at lower frequencies in fatigued muscle. This can persist for several hours to days and is not typically apparent during higher frequencies of post-fatigue stimulation (for review, see Keeton & Binder-Macleod, 2006).

Because very few stimulation studies have addressed the extremely important parameter of intensity, this study specifically compared motor outcomes when using submaximal and supramaximal levels of variable-frequency NMES. Previous investigations support the use of varied frequencies as well as the incorporation of doublets into pulse trains of NMES to prolong force output over time. This study tested the effects of three stimulation patterns: 1) a 20 Hz constant-frequency train, (herein after referred to as 20 Hz train) 2) a 20 Hz single-pulse train that switched to a progressively increasing 20 Hz to 40 Hz train, (20-40 Hz) and 3) a 20 Hz single-pulse train that switched to a 20 Hz doublet pulse train (doublet train) on the fatigue properties of young, healthy thenar muscles of the hand. No study has previously tested these types of stimulation trains at differing stimulation intensities. We hypothesized that greater force output and less fatigue will be present in variable-frequency patterns when compared to a constant-frequency pattern and that force-time integral will not differ when submaximal stimulation levels are compared to supramaximal stimulation levels.

## METHODS

### Participants

A total of ten (10) individuals participated in this study. All were graduate or undergraduate students at the University of Texas at Austin. Five (5) females and five (5) males ranging from 20 to 30 years of age (mean age = 23.81 ± 2.71 years) composed the group. All individuals were of normal health with no physical limitation or significant medical history of neuromuscular or cardiac disorder. Each participant was oriented to the study protocol and signed consent forms prior to any testing. Participation was voluntary, and participants were free to withdraw at any time during the study. All procedures were in compliance with the University of Texas Institutional Review Board policies on Human Subject Research.

### Experimental Setup

Participants were seated in a high-back chair with their right forearm supinated and resting on a tabletop. The shoulder and upper arm were positioned parallel with the trunk and the elbow was positioned at 90º. Hip, knee, and ankle joints were all maintained in a neutral 90º position as well. A custom-designed forearm apparatus made of thermoplastic material (Smith & Nephew, Rolyan, USA) immobilized the forearm and maintained the extremity in a position of supination. The forearm apparatus was attached to a ½” thick sheet of laminated coreboard that was bolted to the laboratory table. Straps secured the forearm at the wrist and forearm midpoint; the upper arm was secured with a strap positioned slightly medial to the elbow that attached to the upper back portion of the chair. The hand was stabilized with therapeutic putty placed underneath, securing the dorsum; putty was placed on the volar surface as well, extending slightly below the metacarpal-phalangeal (MCP) joints to mid-palm. A thermoplastic plate was positioned on the putty over the digits and a strap secured the interphalangeal (IP) joints and the MCP joints in extension. The thumb was extended and abducted and positioned against the force transducer. The custom-designed force transducer device (Mechanical Engineering Shop, University of Texas at Austin) consisted of a mobile, rotating, height-adjustable horizontal arm made of two narrow aluminum surfaces: a vertical surface with a strain gauge that measured the evoked forces of thumb adduction (x), and a horizontal surface with a strain gauge that measured evoked forces of thumb extension (y). A moderate stretch into abduction was placed on the thumb to position it against the transducer surface. The contact area spanned from the thumb tip to midway between the IP and MCP joint. See Figure 1.1 for a graphic of instrumentation setup.

The force output as a result of stimulation emanated directly from the IP joint onto the transducer surfaces. The resultant force, $R = \sqrt{x^2 + y^2}$ was calculated, displayed on the computer monitor, and recorded using commercially-available software (Spike 2, Version 5.14, Cambridge Electronics Design). A stimulating electrode with the anode and cathode 2 cm apart was placed over the median nerve, slightly medial to the wrist and secured with a Velcro band and tape after optimal placement was obtained. Electrical impulses of 50 μs pulse duration were delivered through the stimulating electrode from a constant current stimulator (Digitimer, Ltd., Model DS7A, Welwyn Springs, UK) using custom-written scripts constructed through the Spike 2 software. The electromyographic

(EMG) signal was recorded through two adhesive pre-gelled Ag/AgCl• bipolar surface electrodes 5mm in diameter (Danlee Medical Products, Inc. USA). The active electrode was placed over the thenar eminence slightly medial to the MCP joint of the thumb and the reference electrode approximately 1cm medial to the active electrode. The third (ground) electrode was placed over the pisiform bone.

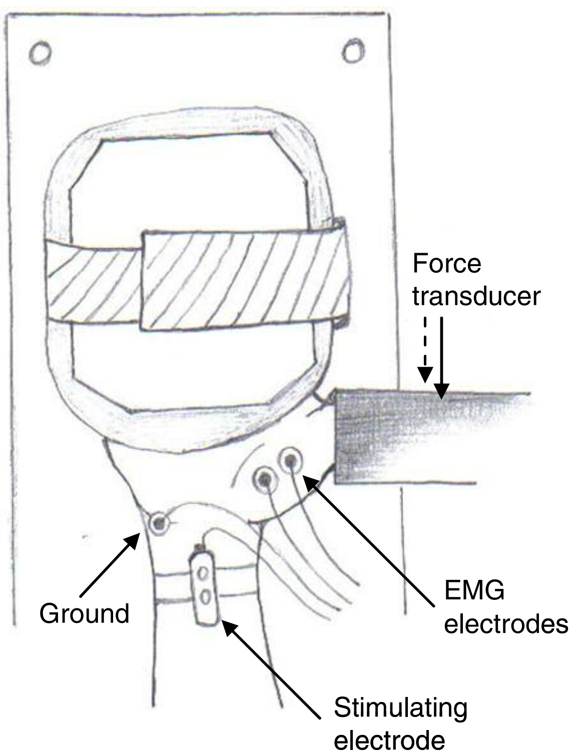


Figure 1.1 Graphic of equipment and positioning for participants.

**Experimental Protocol**

Isometric force output during evoked thumb adduction and extension was investigated using three different types of electrical stimulation trains. All trains used intermittent bursts of 300 ms “on” time and 700 ms “off” time based on the Burke experimental protocol used frequently in neuromuscular electrical stimulation research (Burke, Levine, Tsairis, & Zajac, 1973). Three (3) different fatigue tests consisting of a combination of stimulation trains were administered at supramaximal as well as submaximal stimulation levels, for a total of six sessions. Each session was separated by at least 48 hours to recover from possible effects of low frequency fatigue.

Fatigue Test 1 was the baseline measure and consisted of a 3-minute intermittent 20 Hz train. Fatigue Test 2 consisted of a 3-minute intermittent train that began at 20 Hz, and midway through the protocol (90 seconds), began gradually increasing in frequency from 20 Hz to 40 Hz such that 40 Hz was the terminal frequency reached at 180 seconds. Fatigue Test 3, the doublet train, similarly began at 20 Hz, and midway through the protocol (90 seconds) the pattern changed to a doublet pattern that continued to the end of the train. Figure 2 graphically displays and further explains the three trains used in the three fatigue tests.

Prior to each fatigue test, single 1 Hz pulses were delivered with a pulse width of 50 μs. These pulses were given at various stimulator placements to elicit the maximum compound muscle action potential (M-wave). The M-wave amplitude and twitch were monitored during these pulses. Intensity was progressively increased by 1 μA to obtain maximal M-wave and twitch. For the supramaximal stimulation tests, the current was set approximately 10% higher than the intensity eliciting the maximum M-wave. For the submaximal stimulation tests, an intensity that elicited 20% of the force value obtained during a supramaximal 4-second constant 20 Hz train was used. Initially, the force output at intermittent 1-second 20 Hz trains was monitored and the stimulation intensity was adjusted until reaching the 20% value. A test train of 4-seconds was then delivered to insure that the accurate force level was obtained and was used as a marker of consistency between sessions. This intensity level was then used for the subsequent submaximal fatigue tests.

Once intensity was set, five 1 Hz pulses were administered. This was followed by administration of the 4-second constant 20 Hz train, then three maximal voluntary contractions of thumb adduction (MVCs) lasting approximately 3 seconds each were performed. Interpolated twitches were given during the MVCs to insure maximum voluntary effort. Then 5 random, constant frequency, 4-second trains of 10, 20, 30, and 40 Hz and a 2-second train of 50 Hz were delivered. Each of these trains was separated by 3 seconds. These data were collected to obtain information regarding changes in force at various frequency levels before and after fatigue and to assess whether low frequency fatigue was present. Ten seconds elapsed between the five 1 Hz pulses, the 4-second 20 Hz train, the three MVCs, the five trains of varying frequencies, and before the fatiguing train began. The 3-minute fatiguing stimulation train then followed. One of the three different fatiguing stimulation trains was administered at each session. At the completion of the fatiguing stimulation train, 3s rest elapsed, then the 5 constant frequency trains were again delivered, followed by 3s rest, then repetition of the 3 MVCs. At the completion of all tests, intermittent 1 Hz 50 μs pulses were administered to monitor M-wave changes and recovery. Recovery of M-waves verified stability of the stimulating electrode during testing.

Each of the three experimental sessions followed the same protocol and was identical except for the fatiguing train administered. Participants were stimulated with only one fatigue test per visit (Fatigue Test 1, constant 20 Hz train; Fatigue Test 2, gradually increasing frequency train; or Fatigue Test 3, doublet train) and the order was randomized across participants. See Figure 1.3 for experimental protocol.

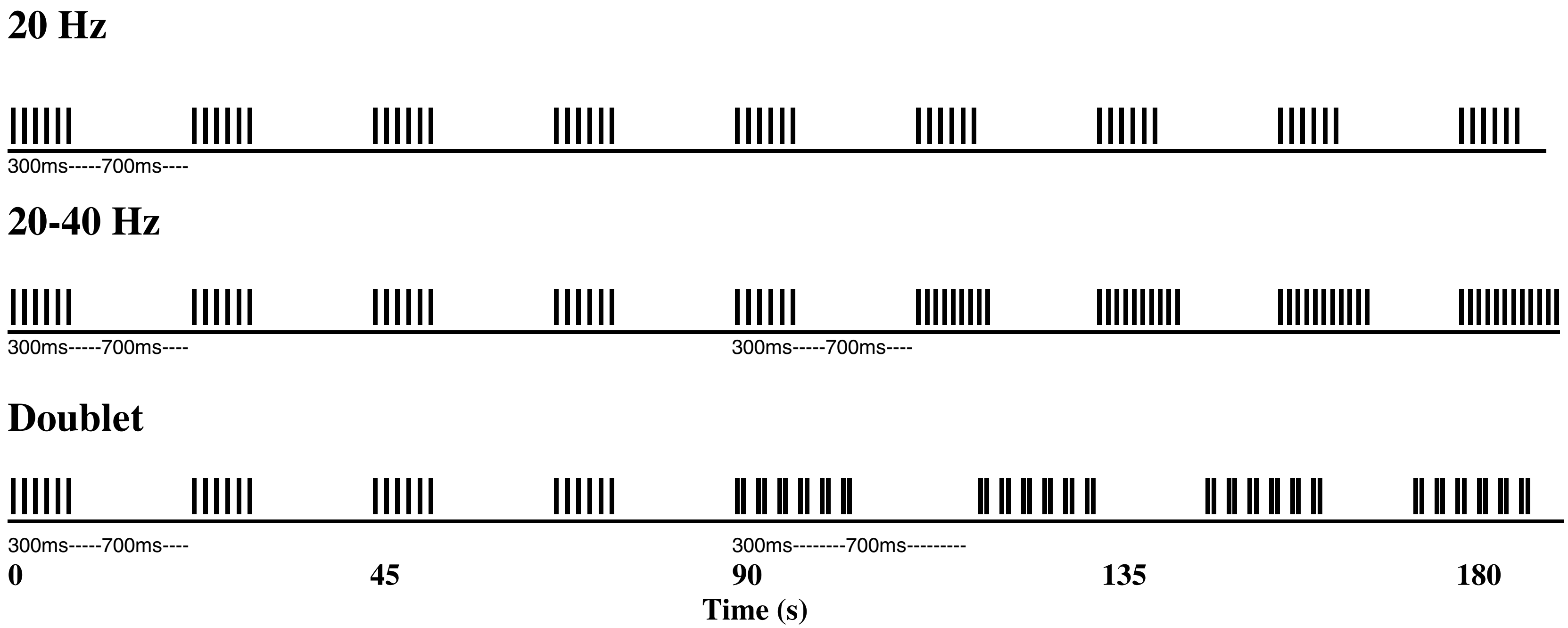


Figure 1.2. 20 Hz: Graphic representation of pulses at 45s time increments during the three, 3-minute fatigue tests: the constant 20 Hz pattern (Fatigue Test 1), the 20-40 Hz increasing pattern (Fatigue Test 2), and the doublet pattern (Fatigue Test 3). All fatigue tests used the Burke (1973) protocol where stimulation is on for 300ms, and off for 700 ms during each second of stimulation.

The force output signal was amplified by 100 (Bridge 8 Amplifier System, Model 74030, World Precision Instruments) sampled at 1000 Hz and low-pass filtered at 1kHz. EMG was amplified by 100, high-pass filtered above 8 Hz, (Coulbourn Instruments Isolated Bioamplifier with Bandpass Filter, Model V75-04) sampled at 2000 Hz, and digitally converted (Micro 1401 mkII 500kHz 16-bit  Analog-Digital Converter with ADC 12 Expansion, Cambridge Electronics Design). All data were recorded and analyzed using Spike 2 software (Version 5.14, Cambridge Electronics Design).

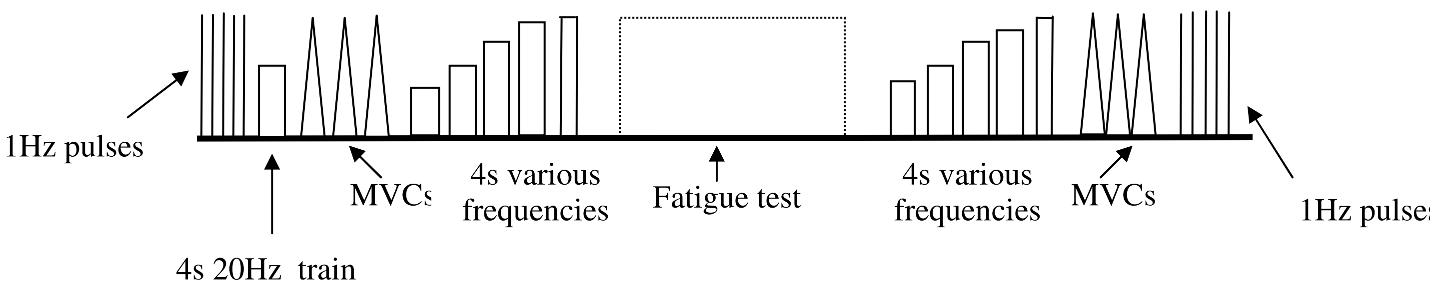


Figure 1.3. Graphic representation of study protocol. The 1Hz pulses, 4s 20Hz train, MVCs and 5 varying frequencies prior to the fatiguing protocol were separated by 10s each. After the fatiguing protocol, 3s elapsed between fatigue protocol, 5 varying frequencies, MVCs, and final 1Hz pulses.

The force output signal was amplified by 100 (Bridge 8 Amplifier System, Model 74030, World Precision Instruments) sampled at 1000 Hz and low-pass filtered at 1kHz. EMG was amplified by 100, high-pass filtered above 8 Hz, (Coulbourn Instruments Isolated Bioamplifier with Bandpass Filter, Model V75-04) sampled at 2000 Hz, and digitally converted (Micro 1401 mkII 500kHz 16-bit  Analog-Digital Converter with ADC 12 Expansion, Cambridge Electronics Design). All data were recorded and analyzed using Spike 2 software (Version 5.14, Cambridge Electronics Design).

**Statistical Analysis**

For day to day reliability testing, two-way repeated measures ANOVAs were used to compare MVCs, 4s 20 Hz constant stimulation trains, and starting forces 10s into the fatiguing stimulation pattern.

Forces at 10s intervals were measured for every stimulation pattern administered. Overall force-time integrals (FTIs), the total area under the fatiguing stimulation train force trace, were computed from the interval measures. These values were calculated in kN•s and are reflective of the total force production during the given fatigue test. Force values were compared using a two-way repeated measures analysis of variance (ANOVA) with stimulation intensity (supramaximal and submaximal) and pattern (20 Hz, 20-40 Hz and doublet) as the independent variables. Tukey's analysis was used for pairwise post-hoc comparisons.

MVCs performed before and after the fatiguing stimulation train were measured and compared with a 3 X 2 X 2 repeated measures ANOVA using pattern (20 Hz, 20-40 Hz, or doublet), intensity (supramaximal or submaximal), and time (pre- or post-fatiguing stimulation pattern) with a post hoc Bonferonni correction.

Maximum evoked forces from each of the five various frequency trains of thumb adduction (10, 20, 30, 40, and 50 Hz) were measured before and after each fatiguing train. These values were compared across the three patterns (20 Hz, 20-40 Hz and doublet), the two stimulation intensities (supramaximal and submaximal), and the two time levels (pre- and post-fatigue). A multivariate analysis of variance (MANOVA) was used for this comparison, with univariate ANOVAs and Bonferroni corrections for post hoc analysis. This determined the effects of pattern, stimulation intensity, and time on evoked contractions of thumb adduction at the five various frequencies and would provide any evidence of low-frequency fatigue. M-wave amplitudes were collected before and after testing and compared using a 3 X 2 X 2 (pattern X intensity X time) repeated measures ANOVA. This analyses was used to ensure that stimulator placement remained stable throughout testing.

An alpha level of 0.05 was used for all statistical comparisons and significance accepted when P • 0.05. All data are presented as mean ± standard deviation throughout the text and mean ± standard error for the tables and figures.

## RESULTS

### Day to Day Repeatability

Average MVC forces collected before the supramaximal 20 Hz, 20-40 Hz, and doublet stimulation were 67.70 ± 8.66 N, 71.00 ± 9.28 N, and 71.67 ± 9.338 N respectively. There was no significant difference in MVCs performed before each of the three fatigue tests. Average MVC forces collected before the submaximal 20 Hz, 20-40 Hz and doublet tests were 67.72 ± 8.71 N, 67.73 ± 9.93 N, and 73.11 ± 10.79 N respectively. There was no significant difference in MVCs prior to each of these fatigue tests as well. No significant difference was present between the two intensity levels.

Additionally, a 4-second 20 Hz stimulation train was administered at the onset of every test and compared across sessions for additional reliability. No significant differences were present in 4s trains presented before each of the three supramaximal fatigue tests. Supramaximal average evoked 4s forces were 19.22 ± 3.24 N (20 Hz), 17.81 ± 3.05 N (20-40 Hz), and 16.48 ± 2.23 N (doublet). Likewise, no significant difference was seen between 4s trains presented before each of the submaximal fatigue tests. Submaximal 4s evoked forces across fatigue tests were 13.28 ± 1.42 N, 14.10 ± 1.52 N and 14.25 ± 1.39 N for the 20 Hz, 20-40 Hz, and doublet patterns respectively. As expected, a significant difference was present between intensities, with supramaximal intensities eliciting significantly higher 4s forces than submaximal intensities (average: 23.53 ± 1.65%; P=0.032).

Starting forces measured at the 10s time interval for fatigue tests were also analyzed for reliability across tests. Starting forces for supramaximal tests were as follows: 12.75 ± 6.09 (20 Hz); 11.61 ± 5.73 (20-40 Hz); and 11.87 ± 2.88 N (doublet). There was no significant difference in starting forces across the supramaximal tests. For the submaximal tests, average starting force for the 20 Hz test was 7.40 ± 3.18; 20-40 Hz, 8.24 ± 3.90; and doublet, 8.55 ± 2.99 N. Comparisons indicated no differences across tests for submaximal intensities as well. Again, supramaximal and submaximal intensities showed expected significant differences. Starting forces at 10s for supramaximal stimulation were significantly higher (average: 32.97 ± 4.53%; P=<0.001) than 10s at submaximal intensities.

**Force and Force-Time Integrals**

Force time integrals (FTI) showed significant overall differences across pattern and stimulation intensity. Figure 1.4 depicts the average forces for every 10s of supramaximal stimulation for all subjects over the three fatiguing stimulation patterns. Average forces for the three supramaximal patterns were as follows: 20 Hz, 9.22 ± 1.76 N; 20-40 Hz, 9.54 ± 1.16 N; and doublet, 8.79 ± 1.77 N. Peak forces for supramaximal patterns were as follows: 20 Hz, 12.98 ± 6.21 N; 20-40 Hz, 12.47 ± 5.86 N; doublet, 13.28 ± 3.15 N. Overall FTI was 1.62 ± 0.01 kN•s for the 20 Hz pattern, 1.69 ±0.01 kN•s for the 20-40 Hz, and 1.54 ± 0.01 kN•s for the doublet pattern. Pairwise comparisons indicated that the FTI for the 20-40 Hz pattern was significantly greater (P=.017) than the doublet pattern at supramaximal intensities. There was no significant difference between the 20 Hz and the 20-40 Hz FTIs at this intensity.

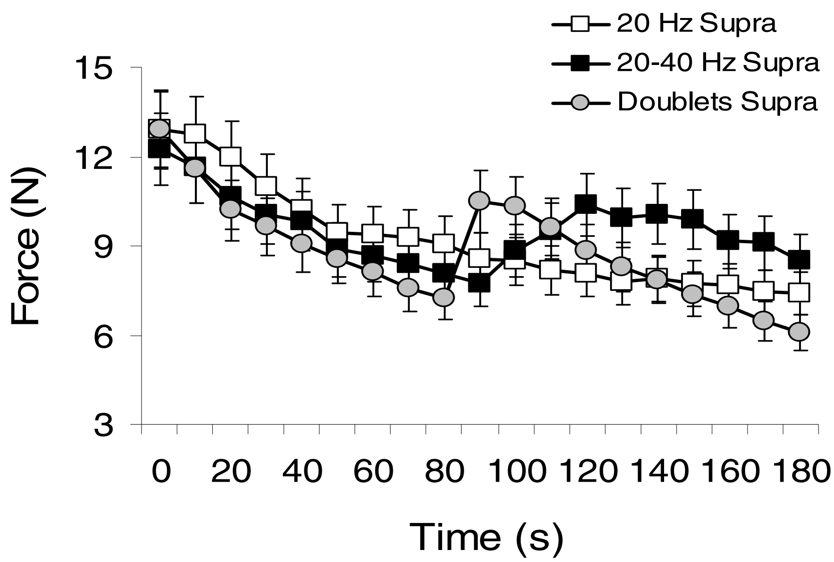


Figure 1.4. Average forces recorded at 10s intervals during the three fatiguing stimulation patterns at supramaximal intensities.

Figure 1.5 depicts the average forces for every 10s of submaximal stimulation patterns. The average force for the 20Hz was 5.99 ± 0.87 N; for the 20-40 Hz, 6.66 ± 0.93 N; for the doublet, 7.89 ± 1.28 N. Peak forces for the 20 Hz, 20-40 Hz, and doublet submaximal patterns were as follows: 8.30 ± 3.30 N, 9.35 ± 3.73 N, and 11.02 ± 3.86 N respectively. Overall FTI for the three submaximal patterns were as follows: 20 Hz, 1.05 ± 0.16 kN•s; 20-40 Hz, 1.17 ± 0.18 kN•s; and doublet, 1.40 ± 0.29 kN•s. The FTI for the doublet pattern was significantly higher ($P<0.001$) than both the 20 Hz and the 20-40 Hz at this intensity level. Figure 1.6 shows both supramaximal and submaximal FTI comparison.

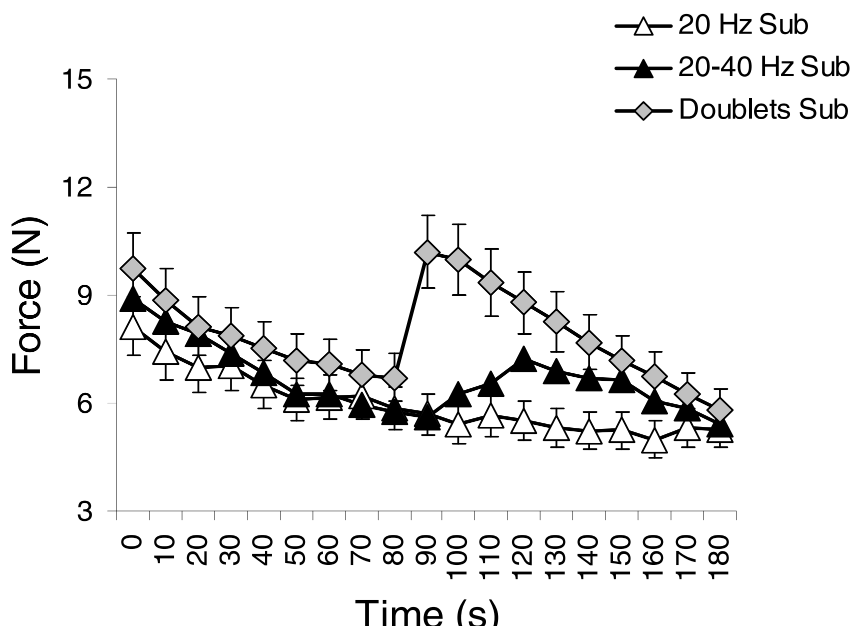


Figure 1.5. Average forces recorded at 10s intervals during the three fatiguing stimulation patterns at submaximal intensities.

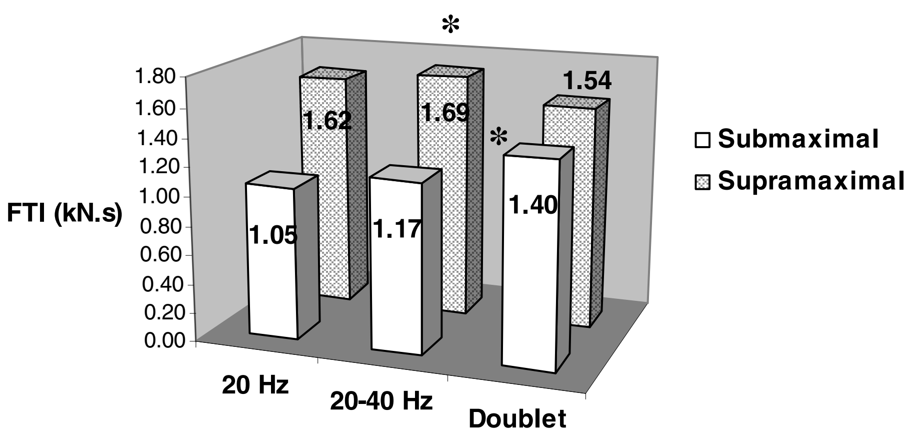


Figure 1.6. Force-time integrals (FTIs) for the three fatiguing stimulation patterns at both intensities.

The doublet pattern immediately increased the force output upon application at the supramaximal intensity (29.64 ± 1.79% increase from preceding pulse) and the submaximal intensity (34.15 ± 3.00% increase). For all participants, a marked difference in force output was apparent from second 89 when compared to second 90 (see Figure 1.7). This increase at 90s can be seen in individual raw data plotted for the ten participants at the submaximal intensity in Figure 1.8. Three representative force traces spanning the time period of 80s through 140s in each stimulation pattern show the changes in force output after the 90s mark in the 20-40 Hz and doublet patterns (Figure 1.9). Nevertheless, all three patterns at both intensities showed a decline in force from onset to termination. Forces at the end of the supramaximal stimulation patterns had declined 42.76 ± 4.32% from initial for 20 Hz; 30.52 ± 3.00% from initial for 20-40 Hz; and 52.79 ± 4.36% from initial for the doublet pattern. The decline in force from onset to termination at the submaximal intensity was 34.97 ± 3.35% initial for the 20 Hz, 39.50 ± 3.31% initial for the 20-40 Hz, and 40.41 ± 4.18% initial for the doublet.

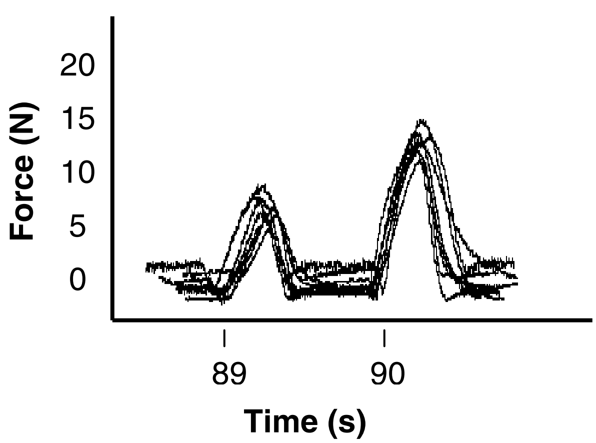


Figure 1.7. Stimulation pulses at second 89 and second 90 during the submaximal doublet stimulation protocol. Doublet pulses began at second 90. Force traces of all ten participants have been overlaid.

**Maximal Voluntary Contractions**

Maximal voluntary contractions (MVCs) performed before and after the three fatiguing patterns at the supramaximal intensity showed an average decrease in voluntary strength of 7.60 ± 0.10% MVC for the 20 Hz pattern, 9.67 ± 0.09% MVC for the 20-40 Hz pattern, and 10.91 ± 0.09% MVC for the doublet pattern. MVCs performed before and after the three submaximal fatiguing patterns showed an average decrease in voluntary strength of 6.10 ± 0.02% MVC for the 20 Hz pattern, 8.16 ± 0.01% MVC for the 20-40 Hz pattern, and 6.77 ± 0.01% MVC for the doublet pattern. Differences in MVCs performed prior to each fatigue test compared to MVCs performed after each fatigue test (factor: time) were significant at the P=0.001 level. Force losses in maximal voluntary contractions were generally similar across patterns and intensities, with no significant differences present in these measures.

**Force-Frequency Distributions**

Averaged force data from the 10, 20, 30, 40 and 50 Hz trains for each pattern at each intensity can be seen in Figure 1.10. Forces at the 5 different frequencies were similar across patterns, but significantly different across intensities (P=0.004). Supramaximal intensities showed higher average forces when compared to submaximal intensity forces: 10 Hz, 9.07 ± 0.36 vs. 8.01 ± 0.93 N; 20 Hz, 16.82 ± 0.58 vs. 14.55 ± 0.59 N; 30 Hz, 20.87 ± 0.75 vs. 17.86 ± 0.62 N; 40 Hz, 22.73 ± 1.36 vs. 19.46 ± 0.85 N; and 50 Hz, 23.41 ± 1.45 vs. 20.06 ± 0.94 N.

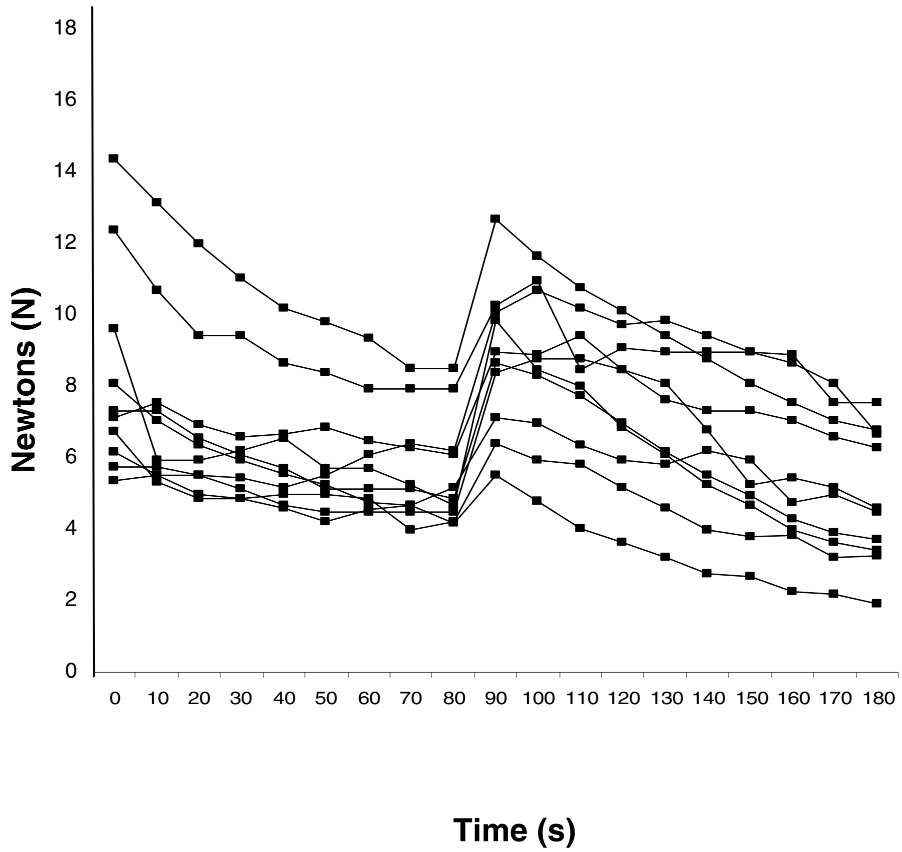


Figure 1.8. Raw data indicating force levels at 10s time increments during the submaximal doublet stimulation protocol. A notable increase in force is evident at second 90 for all participants.

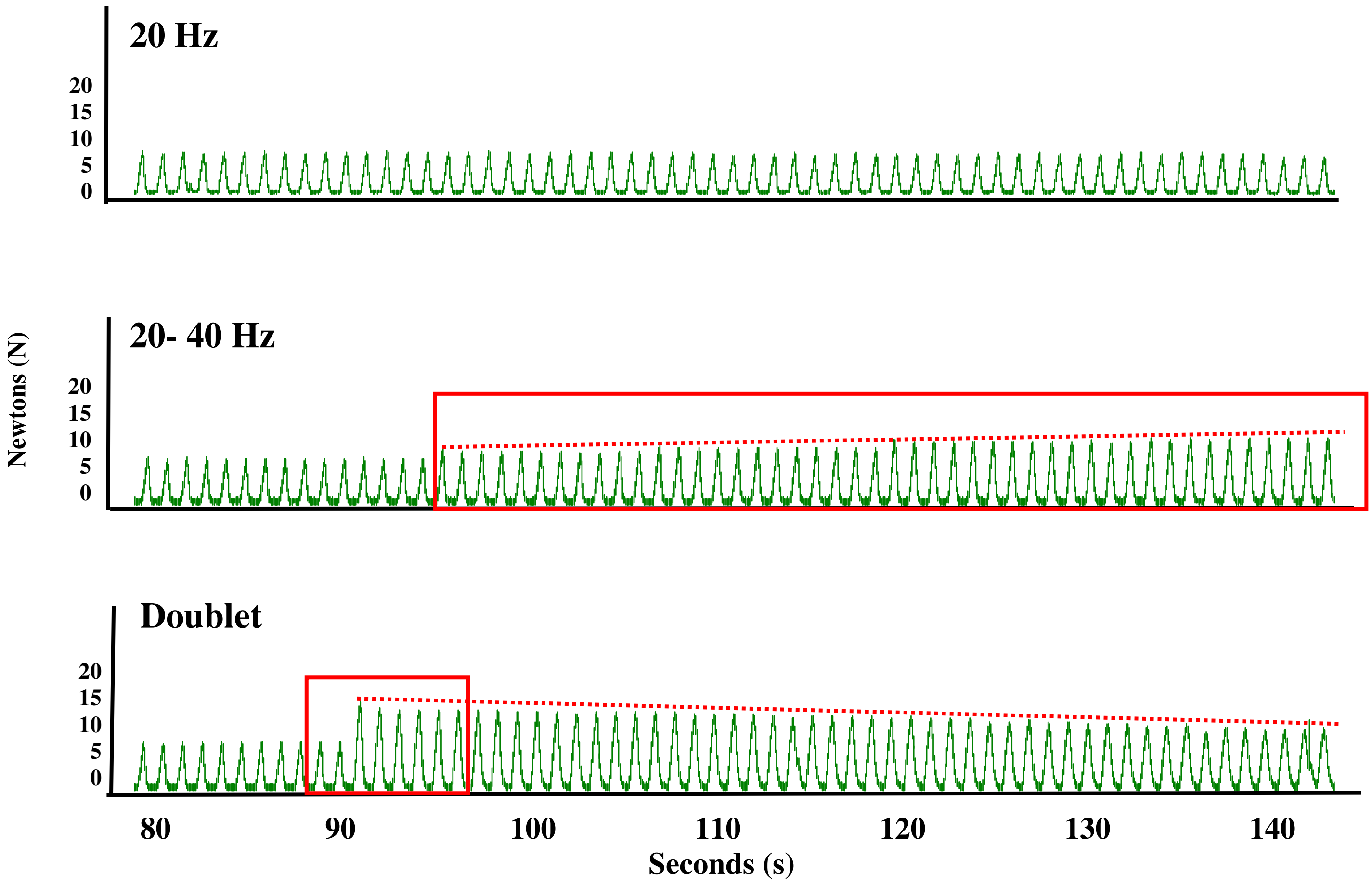


Figure 1.9. Raw data of one representative subject showing the three fatiguing stimulation patterns at a supramaximal intensity (A. 20 Hz, B. 20-40 Hz, and C. Doublet) during the 80 to 140s time period of the 3-minute pattern. The stimulation pattern change occurred at the 90s mark for B and C. A gradual increase in force output can be seen in B following the change of pattern (red box); an immediate and rapid increase in force is apparent in C (red box) at the pattern change.

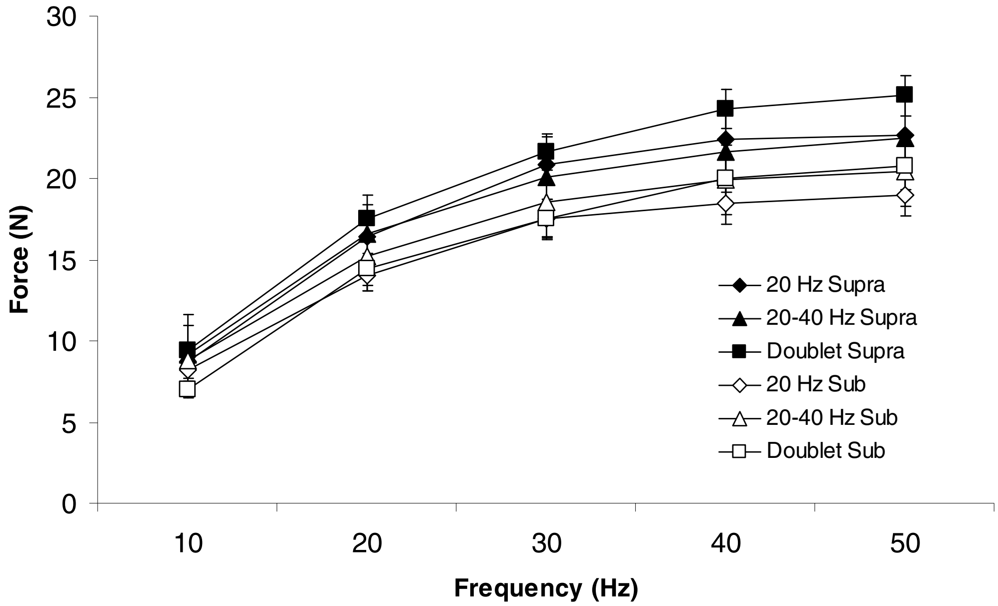


Figure 1.10. Average forces recorded during the 4s constant frequency trains of 10, 20, 30, 40, and 50 Hz for all stimulation patterns at both intensities.

Percentage decreases in the five evoked forces at the various frequencies (10, 20, 30, 40, and 50 Hz) from pre-fatiguing train to post-fatiguing train are shown in Figure 11. Both intensities are presented. Statistical analysis indicated a significant overall effect of frequency ($P = 0.036$), with the 10 Hz frequency train showing significantly greater force loss when compared to the remaining trains. Pattern showed an overall significant effect ($P = 0.05$) without significant pairwise interactions. Time was also a significant factor with all five frequency trains showing significant changes from pre-fatigue to post-fatigue values ($P < 0.001$). No overall differences were seen between the two intensities.

**M-Wave Amplitude**

M-wave amplitudes were measured prior to testing and at the completion of all tests to ensure stability of the stimulating electrode. Average m-wave values before and after stimulation at the supramaximal intensity were as follows: 20 Hz, 1.20 ± 0.61 pre, 1.18 ± 0.55 mV post; 20-40 Hz, 0.93 ± 1.05 pre, 0.83 ± 0.96 mV post; doublet, 1.21 ± 0.81 pre, 1.12 ± 0.87 mV post. Average m-wave values before and after stimulation at the submaximal intensity were 1.16 ± 0.61 pre, 1.14 ± 0.59 mV post for the 20 Hz pattern, 0.68 ± 0.84 pre, 0.67 ± 0.79 mV post for the 20-40 Hz pattern, and 0.88 ± 1.09 pre, 0.87 ± 1.01 post for the doublet pattern. The 3 X 2 X 2 repeated measures ANOVA indicated no significant overall differences in pre-post values, validating consistency in electrode placement and stability. Additionally, no significant differences were present between patterns or intensity. Submaximal to supramaximal m-wave ratios were calculated and indicated an average of approximately 85% for all tests (20 Hz pre, 81.97 ± 0.42; 20 Hz post, 78.63 ± 0.63; 20-40 Hz pre, 84.61 ± 0.54; 20-40 Hz post, 84.45 ± 0.47; doublet pre, 89.67 ± 0.38; doublet post, 88.31 ± 0.38).

## DISCUSSION

The purpose of this study was to compare differences in force output when variable stimulation patterns were administered at supramaximal and submaximal intensity levels. Because the majority of investigations have used submaximal stimulation intensities that target only a limited number of muscle fibers, we wanted to compare any differences that would exist when variable patterns are applied at supramaximal intensities where a maximum number of fibers are activated. We tested the effects of three patterns: 1) a 20 Hz constant-frequency train, 2) a 20 Hz single-pulse train that switched to a progressively increasing 20 Hz to 40 Hz train, and 3) a 20 Hz single-pulse train that switched to a 20 Hz doublet pulse train (doublet train) applied to the thenar muscles of young, healthy individuals applied at both intensities.

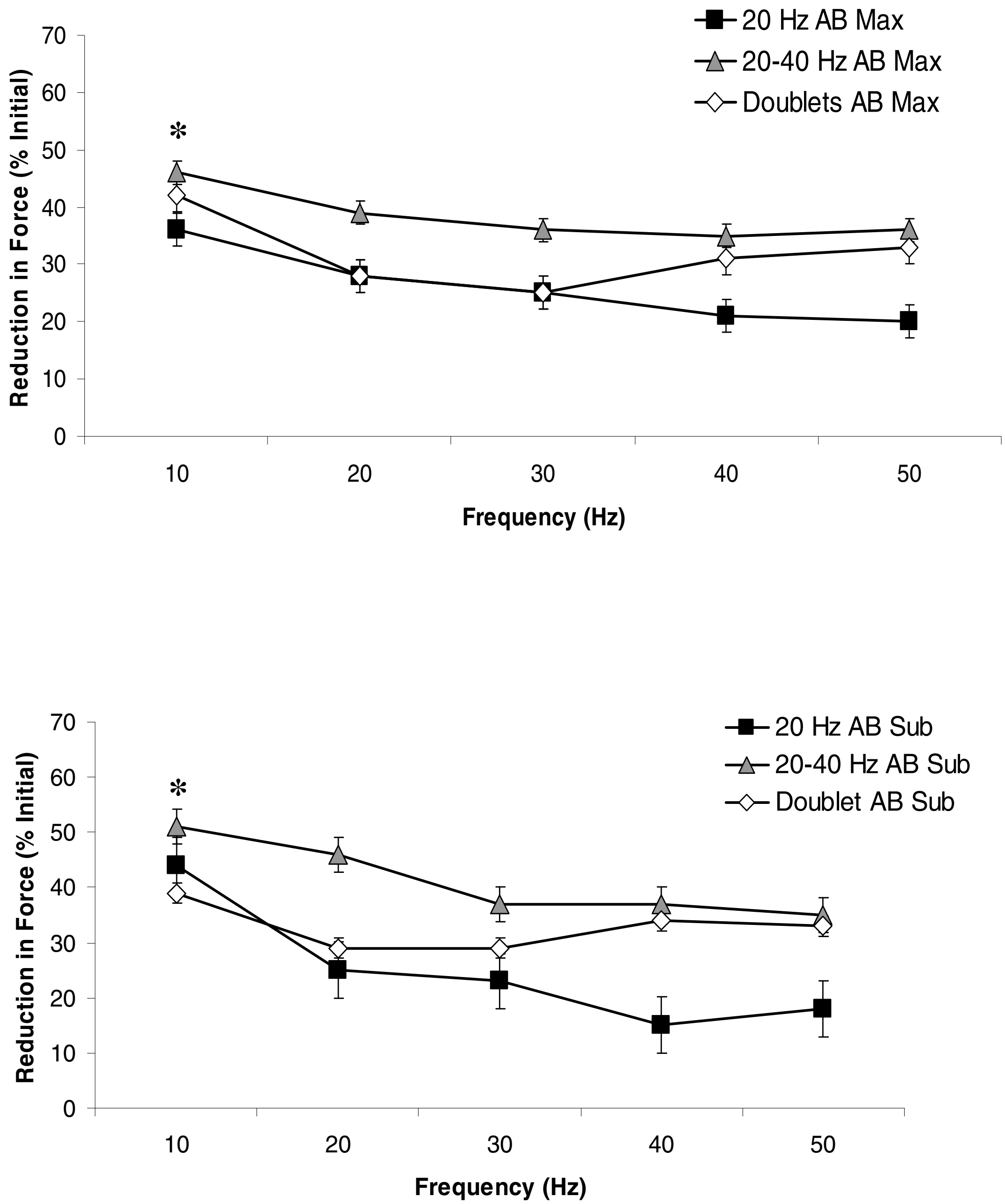


Figure 1.11. Force vs. frequency curves based on changes of constant frequency trains of 10, 20, 30, 40, and 50 Hz administered before and after each fatiguing stimulation pattern at both intensities. Top graph, supramaximal intensities, bottom graph, submaximal intensities. Force loss at 10 Hz was significantly greater than force loss at remaining frequencies at both intensities.

In this investigation, supramaximal and submaximal stimulation intensities generated different results. At supramaximal intensities, the progressively increasing pattern (20-40 Hz) showed overall higher average forces and a higher overall FTI; however, at submaximal intensities, the doublet pattern produced the highest average forces, and the highest overall FTI. Godfrey et al. (2002) compared the effect of submaximal and supramaximal stimulation of motor units in paralyzed thenar muscle and found that force loss, FTI decline and slowing of half-relaxation time were significantly lower during submaximal stimulation. Preston et al. (1994) measured conduction velocity at various sites along the ulnar nerve using submaximal and supramaximal stimulation. They concluded that because submaximal stimulation tends to target larger and faster motor units and the topography of the nerve may be different at various sites, submaximal stimulation did not yield consistent results and supramaximal stimulation is a more valid method. Early work by Davies, Mecrow, and White (1982) saw notable differences during submaximal stimulation intensities when compared to supramaximal while exploring the effects of heating the triceps surae muscle in a young healthy population. Heating of muscle prior to stimulation at submaximal intensities enhanced twitch and tetanic tension, while at supramaximal intensities, heating reduced titanic tension. They, too, recommended that the use of supramaximal stimulation is a more reliable measure and should be used when studying contractile properties of human muscle.

Our finding that force is enhanced with the use of doublets during submaximal stimulation intensities is consistent with previous studies. Submaximal stimulation trains that are initiated with a doublet have been shown to produce greater FTIs after fatigue. Binder Macleod, Lee, and Baadte (1997) found that initiating a stimulation train with a doublet using a 5 ms interpulse interval preserved the rate of rise of force in fatigued muscle; a decrease was seen when a constant frequency train was used. In addition, Scott et al. (2003) measured the number of times a targeted isometric force was reached after healthy quadriceps muscles were fatigued with submaximal constant frequency trains, doublet trains, or a combination pattern that incorporated both type of trains. The combination pattern began with a constant frequency and changed to a doublet pattern at a point of fatigue, reaching the targeted forces more often and producing a lower fatigue response. The repetitive use of doublets produced the greatest fatigue response and fewer successful target forces; however, notable enhancement in force was seen when the doublet pattern was activated after the constant frequency pattern. We similarly found this same effect in our doublet pattern at submaximal intensities.

Dynamic muscle performance in healthy quadriceps has been enhanced through the use of variable patterns used at submaximal intensities. Doublet trains and doublet-initiated trains produced greater excursions of knee extension when compared to a constant frequency trains (Maladen et al, 2006). Variable stimulation trains have optimized force output when used at maximal stimulation intensities as well. Shields et al. (2006) used a feedback-controlled system such that a variable stimulation pattern was activated when paralyzed soleus muscle became fatigued following repetitive contractions. At the point where ankle torque output declined by 10%, one of three variable stimulation patterns was activated: a fixed increase in frequency, a doublet-initiated train, or a fixed decrease in frequency. They found that the increasing frequency pattern was most effective in maximizing torque output in this population. Our results also supported the effectiveness of using an increasing frequency pattern to enhance force output at a point of fatigue during supramaximal stimulation. These results therefore suggest that the use of a combination stimulation pattern where an alteration of pulses occurs at a point of fatigue may be effective in enhancing overall muscle performance.

We incorporated similar parameters into this study, using a 20 Hz single pulse pattern that changed to a doublet pattern or an increasing frequency pattern at supramaximal and submaximal intensities. The 20 Hz single pulse pattern was a high enough frequency to maintain tetany and force output yet delay the onset of fatigue. Previous work using a 20 Hz stimulation in healthy thenar muscle showed force loss at 90s to be approximately 25% of initial force onset value (Thomas et al., 2003); our data indicated similar decreases in force with a 31.20 ± 2.52 % decrease apparent at the 90s mark. At this time period, the stimulation switched patterns to an increasing frequency or doublet pattern.

In previous work from our laboratory, 3-minute continuous trains that increased (20-40 Hz) or decreased (40-20 Hz) frequency at the *onset* of stimulation at supramaximal intensities showed no differences in overall FTI when compared to a constant 20 Hz pattern (Griffin et al., 2006). Our current findings are similar at supramaximal intensities in that there was no significant difference in overall FTI between the 20 Hz and the 20-40 Hz increasing pattern even when the change in pattern occurred at a point where approximately 30% of initial force had been lost.

Vigreux, Cnockaert, & Pertuzon, (1980) found that muscle which has already become fatigued and decreased in overall contractility and stiffness typically responds favorably to a change in firing rate or recruitment of motor units to restore tension and force output. Both the 20-40 Hz pattern and the doublet pattern may have taken advantage of this reduced stiffness condition and showed force enhancement with the change of pattern. However, the increasing frequency pattern in the present study showed more effective force output over time than did the doublet pattern at the supramaximal intensity. Force increased at the onset of the doublet pattern, but rapid fatigue ensued as demonstrated by a fast and steady drop in force immediately thereafter. In contrast, the 20-40 Hz pattern maintained force better following the pattern change and may have done so due to its similarity to natural motor unit firing patterns. This indicates that doublet stimulation at supramaximal intensities may be physiological “overkill” and may further clarify why the benefits of doublet stimulation are only present when submaximal protocols are used.

The onset of the doublet pattern created an exaggerated response when the muscle was generating low-force in a partially fatigued state. This phenomenon was originally identified as a “catch property” by Burke, Rudomin, & Zajac (1970) when they observed the behavior in the muscles of cats. Additionally, while investigating single motor units in the foot, Macefield et al. (1996) found that a doublet-initiated train was only effective if the preceding train was at frequencies of 20 Hz or less. We preceded our doublet trains with a 20 Hz stimulation pattern and likewise obtained enhanced force output and a higher FTI at submaximal intensities. However, when this same pattern was used at a supramaximal level of stimulation, the results were quite different. At supramaximal intensities, a force increase was present, but to a much lesser extent. It is possible that the use of submaximal stimulation intensities may enhance the beneficial effect of doublet stimulation due to the overall lower forces which are present and the greater availability of additional motor units to recruit to augment force.

Parmiggiani and Stein (1981) suggested that the rapid pulses of a doublet impart a forceful tightening of the series elastic element in the fatigued muscle. This state is said to be maintained when single, lower frequency pulses follow (Binder-Macleod & Lee, 1996). Two pulses with short interspike intervals have the potential to increase immediate available calcium (Duchateau & Hainaut, 1986) and therefore could cause the precipitous spike in force we observed during submaximal stimulation, especially when force levels from the onset of stimulation are relatively low. Repetitive and prolonged tetanic stimulation, however, has been shown to keep calcium levels high within intracellular spaces for extended periods when studied in animal models and may, in turn, decrease SR release of calcium when muscle becomes fatigued (Chin, Balnave, & Allen, 1997). Decreased SR calcium release could suppress large increases of force, especially during prolonged doublet stimulation at a supramaximal intensity.

It is possible that fast motor units not previously active were activated at the onset of doublets during our submaximal stimulation protocol and quickly fatigued thereafter. During supramaximal stimulation, maximal numbers of motor units are activated and are firing at maximal rates; therefore, no further recruitment or significant activation was possible. At such high levels of recruitment and firing rate, rapid fatigue develops, which could have produced the precipitous decline in force we observed.

The 4-second evoked forces at frequencies of 10, 20, 30, 40, and 50 Hz were included in this investigation to determine if low frequency fatigue (Edwards et al., 1977) was present following administration of our fatiguing patterns. Given the low frequency fatigue phenomenon, lower frequencies (e.g., 10 Hz and 20 Hz) would be more significantly depressed following the fatiguing stimulation pattern relative to the changes seen in the higher frequencies (30, 40 or 50 Hz) following fatigue. Significant overall differences were present on this measure in frequency and pattern. The greatest amount of force loss was present at the 10 Hz frequency, which suggests the presence of low-frequency fatigue at the 10 Hz level. Furthermore, the LFF response obtained may be influenced by the pulse pattern used. Our protocols used a 20 Hz stimulation pattern which is a low enough frequency to potentially induce low-frequency fatigue effects. This further strengthens the need for the use of higher frequencies to avoid excessive depression of force after muscle has become fatigued.

Researchers have found instances during voluntary fatiguing contractions when M-wave amplitudes do not decline (Bigland-Ritchie, Kukulka, Lippold, & Woods, 1982) or decline minimally at onset but remain stable thereafter (Thomas, Woods, Bigland-Ritchie, 1989) despite the deterioration of force. These studies concluded that force loss was probably not due to neuromuscular block, but rather failure of processes within the muscle fibers. In our study, we found that M-waves generally remained high before and after the fatiguing stimulation patterns, indicating continued excitation of the sarcolemma throughout the protocol. Current evidence suggests that sarcolemmal excitation can remain high during muscle fatigue and the associated force loss may be attributable to increased levels of inorganic phosphate that impair calcium handling and ultimately affect cross-bridge cycling (Stackhouse et al., 2001).

This study revealed that administration of three varying patterns of neuromuscular electrical stimulation applied to the median nerve at supra- and submaximal levels of intensity yielded different results. At supramaximal levels, a steadily increasing pattern (20-40 Hz) proved to be most efficient with the highest FTI. In contrast, when submaximal intensities were used, a doublet pattern showed the greatest efficiency with higher a FTI, similar to what has been demonstrated by others (Scott, et al., 2007; Scott Bickel et al., 2004). It appears that the beneficial effects of applying doublet patterns are greatest when used once to initiate or enhance force output after submaximal intensities are presented and fatigue has begun; however, a repetitive presentation of doublets may augment a greater fatigue response as well, as others have reported (Scott, Lee, Johnston, & Binder-Macleod, 2005).

In summary, the use of submaximal intensities of stimulation yields very different force responses when compared to supramaximal intensities. The results of this study confirm that variable NMES stimulation patterns continue to be more effective in extending force output over time than constant stimulation patterns at either a supramaximal or submaximal intensity. We further suggest that the application of variable stimulation patterns, particularly patterns incorporating doublet pulses, may be enhanced or exaggerated when submaximal intensities are used because overall forces are lower and a cellular environment responsive to rapid force enhancement exists. In contrast, at supramaximal stimulation intensities, force output appears to be optimally enhanced using patterns of stimulation that increase later in the task, similar to what occurs in normal physiological motor unit firing. Additionally, because supramaximal intensities activate a larger number of muscle fibers and extraneous experimental variables are better controlled, this response may be more reflective of whole muscle behavior.

The outcomes of this investigation can have significant implications for applied science. The use of neuromuscular electrical stimulation for rehabilitation of pathological populations and paralyzed individuals has shown to be effective, but until specific patterns and parameters that maximize force output and delay the onset of fatigue can be defined, further study is warranted. We revealed that notable differences are present between submaximal and supramaximal intensities of stimulation. These differences have the potential to impact clinical outcomes. Furthermore, the results of our investigation also suggest that the use of electrical stimulation programs that vary in frequency, incorporate doublets, and more closely simulate physiological motor unit firing patterns may be more effective in maintaining force output and delaying the onset of fatigue, a crucial factor in any rehabilitation effort.

## REFERENCES


Allman, B. L., Cheng, A. J., & Rice, C. L. (2004). Quadriceps fatigue caused by catchlike-inducing trains is not altered in old age. *Muscle and Nerve, 30* (6), 743-751.

Allman, B. L., & Rice, C. L. (2001). Incomplete recovery of voluntary isometric force after fatigue is not affected by old age. *Muscle and Nerve 24* (9), 1156-1167

Allman, B. L., & Rice, C. L. (2004) An age-related shift in the force-frequency relationship affects quadriceps fatigability in old adults. *Journal of Applied Physiology, 96* (3):1026-1032.

Adam, A. & DeLuca, C. J. (2005). Firing rates of motor units in human vastus lateralis muscle during fatiguing isometric contractions. *Journal of Applied Physiology, 99* (1), 268-280.

Baker, L. L., Wederich, C. L., McNeal, D. R., Newsam, C., & Waters, R. L. (2000). *Neuromuscular electrical stimulation,* (4th Ed.). Los Amigos Research & Education Institute: Downey, CA.

Baldwin, E. R., Klakowicz, P. M., & Collins, D. F. (2006). Wide-pulse-width, high-frequency neuromuscular stimulation: implication for functional electrical stimulation. *Journal of Applied Physiology, 101* (1),228-240.

Bellemare, F., & Garzaniti, N. (1988). Failure of neuromuscular propagation during human maximal voluntary contraction. *Journal of Applied Physiology, 64* (3), 1084-1093.

Bergstrom & Hultman (1990). Contraction characteristics of the human quadriceps muscle during percutaneous electrical stimulation. *Pfluger's Archives, 417* (2), 136-141.

Bevan L,  Laouris Y, Reinking R.M., Stuart D.G.(1992). The effect of the stimulation pattern on the fatigue of single motor units in adult cats. *Journal of Physiology, 449,* 85-108.

Bickel, C. S., Slade, J. M., Warren, G. L., & Dudley, G. A. (2003). Fatigability and variable-frequency train stimulation of human skeletal muscles. *Physical Therapy. 83* (4), 366-373.

Bigland-Ritchie, B., Kukulka, C. G., Lippold, O. C., & Woods, J. J.(1982). The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. *Journal of Physiology, 330,* 265-278.

Bigland-Ritchie, B., Jones, D. A., & Woods, J. J. (1979). Excitation frequency and muscle fatigue: electrical responses during human voluntary and stimulated contractions. *Experimental Neurology, 64* (2), 414-427.

Bigland-Ritchie, B., Zijdewind, I., & Thomas, C. K. (2000). Muscle fatigue induced by stimulation with and without doublets. *Muscle and Nerve, 23* (9), 1348-1355.

Binder-Macleod, S. A., & Barker, C. B. (1991). Use of a catchlike property of human skeletal muscle to reduce fatigue. *Muscle and Nerve. 1991, 14* (9), 850-857.

Binder-Macleod S. A., & Guerin, R. (1990). Preservation of force output through progressive reduction of stimulation frequency in human quadriceps femoris muscle. *Physical Therapy, 70* (10), 619-625.

Binder-Macleod, S. A., & Lee, S. C. (1996) Catchlike property of human muscle during isovelocity movements. *Journal of Applied Physiology, 80* (6), 2051-2059.

Binder-Macleod, S. A., & McDermond (1992). Changes in the force-frequency relationship of the human quadriceps femoris muscle following electrically and voluntarily induced fatigue. *Physical Therapy, 72* (2), 95-104.

Binder-Macleod, S. A., & Russ, D. W. (1999) Effects of activation frequency and force on low-frequency fatigue in human skeletal muscle. *Journal of Applied Physiology, 86* (4), 1337-1346.

Binder-Macleod, S. A., & Scott W. B.(2001). Comparison of fatigue produced by various electrical stimulation trains. Acta Physiologica Scandinavia, 172 (3), 195-203.

Binder-Macleod, S. A., Halden, E. E., & Jungles, K. A. (1995). Effects of stimulation intensity on the physiological responses of human motor units. *Medical Science and Sports Exercise, 27* (4), 556-565.

Binder-Macleod, S. A., Lee, S. C., & Baadte, S. A. (1997). Reduction of the fatigue-induced force decline in human skeletal muscle by optimized stimulation trains. *Archives of Physical Medicine and Rehabilitation, 78* (10), 1129-1137.

Binder-Macleod, S. A., Lee, S. C., Russ, D. W., & Kucharski, L. J. (1998). Effects of activation pattern on human skeletal muscle fatigue. *Muscle & Nerve, 21,* 1145-1152.

Binder-Macleod, S. A., & Scott, W. B. (2001). Comparison of fatigue produced by various electrical stimulation trains. *Acta Physiologica Scandinavia, 172,* 195-203.

Boerio, D., Jubeau, M., Zory, R., Maffiuletti, N. A. (2005). Central and peripheral fatigue after electrostimulation-induced resistance exercise. *Medicine & Science in Sport and Exercise, 37* (6), 973-978.

Burke R. E., Levine D. N., Tsairis, P., Zajac, F. E. (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. Journal of Physiology, 234 (3), 723-48.

Burke, R. E., Rudomin, P, & Zajac, F. E., (1970). Catch property in single mammalian motor units. *Science*, *168* (927), 122-124.

Conwit, R. A., Stashuk, D., Suzuki, H., Lynch, N., Schrager, M., & Metter, E. J. ( 2000). Fatigue effects on motor unit activity during submaximal contractions. *Archives of Physical Medicine and Rehabilitation, 81* (9), 1211-1216.

Dorfman, L. J., Howard, J. E., & McGill, K. C. (1990). Triphasic behavioral response of motor units to submaximal fatiguing exercise. *Muscle and Nerve, 13* (7), 621-628.

Duchateau, J. & Hainaut, K. (1986). Nonlinear summation of contractions in striated muscle I. Twitch potentiation in human muscle**.** *Journal of Muscle Research & Cell Motility, 7*(1), 11-17.

Edwards, R. H., Hill, D. K., Jones, D. A., & Merton, P. A. (1977). Fatigue of long duration in human skeletal muscle after exercise. *Journal of Physiology (London), 272,* 769-778.

Fuglevand, A. J., Zackowski, J. M., Huey, K. A. & Enoka, R. M. (1993) Impairment of neuromuscular propagation during human fatiguing contractions at submaximal forces. *Journal of Physiology, 460,* 549-572.

Fuglevand, A. J., Macefield, V. G., & Bigland-Ritchie, B. (1999). Force-frequency and fatigue properties of motor units in muscles that control digits of the human hand. *Journal of Neurophysiology, 81,* 1718-1729.

Fuglevand, A. J., Keen, D. A. (2003). Reevaluation of muscle wisdom in the human adductor pollicis using physiological rates of stimulation. *Journal of Physiology, 549,* 865-75.

Garland, S. J., Griffin, L., Ivanova, T. (1997). Motor unit discharge rate is not associated with muscle relaxation time in sustained submaximal contractions in humans. Neuroscience Letters, 239, 25-28.

Godfrey, S., Butler, J. E., Griffin, L., & Thomas, C. K. (2002). Differential fatigue of paralyzed thenar muscles by stimuli of different intensities. *Muscle and Nerve, 26* (1), 122-131.

Gorgey, A. S., Mahoney, E., Kendall, T., & Dudley, T. J. (2006). Effects of neuromuscular electrical stimulation parameters on specific tension. *European Journal of Applied Physiology, 97* (6), 737-744.

Gregory, C. M., Dixon, W., & Bickel C. S. (2007). Impact of varying pulse frequency and duration on muscle torque production and fatigue. *Muscle and Nerve, Jan 17* [Epublished ahead of print].

Griffin, L., Godfrey, S. & Thomas, C. K. (2002). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. *Journal of Neurophysiology, 87*, 2271-2278.

Griffin, L., Jun, B. G., Covington, C., & Doucet, B. M. (2006) [In press]. Force output during fatigue with progressively increasing stimulation frequency. *Journal of Electromyography & Kinesiology.*

Hanchard, N. C. A., Williamson, M, Caley, R. W., and Cooper, R. G. (1998). Electrical stimulation of human tibialis anterior: (A) contractile properties are stable over a range of submaximal voltages; (B) high- and low-frequency fatigue are inducible and reliably assessable at submaximal voltages. *Clinical Rehabilitation, 12,* 413-427.

Karu, Z. Z., Durfee, W. K., & Barzilai, A. M. (1995). Reducing muscle fatigue in FES applications by stimulating with N-let pulse trains. *IEEE Transcripts of Biomedical Engineering, 42*(8), 809-817.

Kebaetse, M. B., & Binder-Macleod, S. A. (2004). Strategies that improve human skeletal muscle performance during repetitive, non-isometric contractions. *Pflugers Archives, 448*(5), 525-32.

Kebaetse, M. B., Lee, S. C., & Binder-Macleod, S. A. (2001) A novel stimulation pattern improves performance during repetitive dynamic contractions. *Muscle and Nerve, 24* (6), 744-752.

Kebaetse, M. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Strategies that improve paralyzed human quadriceps femoris muscle performance during repetitive, nonisometric contractions. *Archives of Physical Medicine and Rehabilitation, 86* (11), 2157-2164.

Kebaetse, M. B., Turner, A. E., & Binder-Macleod, S. A. (2002). Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. *Journal of Applied Physiology, 92* (1), 109-116.

Keeton, R. B., & Binder-Macleod, S. A. (2006). Low-frequency fatigue. *Physical Therapy, 86* (8), 1146-1150.

Kesar, T. & Binder-Macleod, S. A. (2006). Effect of frequency and pulse duration on human muscle fatigue during repetitive electrical stimulation. *Experimental Physiology, 91*, (6), 967-976.

Kesar, T., Chou, L. W., & Binder-Macleod, S. A. (2007). Effects of stimulation frequency versus pulse duration modulation on muscle fatigue. *Journal of Electromyography & Kinesiology, Feb 20,* [Epublished ahead of print].

Laufer, Y., Ries, J. D., Leininger, P. M., & Alon, G. (2001). Quadriceps femoris muscle torques and fatigue generated by neuromuscular electrical stimulation with three different waveforms. *Physical Therapy, 81* (7), 1307-1316.

Lee, S. C., Becker, C. N., & Binder-Macleod, S. A. (2000). Activation of human quadriceps femoris muscle during dynamic contractions: effects of load on fatigue. *Journal of Applied Physiology, 89* (3), 926-936.

Lee, S. C., & Binder-Macleod, S. A. (2000). Effects of activation frequency on dynamic performance of human fresh and fatigued muscles. *Journal of Applied Physiology,88* (6), 2166-2175.

Lieber, R. L, & Kelly, M. J. (1996). Torque history of electrically stimulated quadriceps: Implications for stimulation therapy. *Journal of Orthopedic Research, 11* (1), 131-141.

Macefield, V. G., Fuglevand, A. J., & Bigland-Ritchie, B. (1996). Contractile properties of single motor units in human toe extensors assessed by intraneural motor axon stimulation. *Journal of Neurophysiology,75* (6), 2509-2519.

MacIntosh, B. R., & Willis, J. C. (2000). Force-frequency relationship and potentiation in mammalian skeletal muscle. *Journal of Applied Physiology, 88*(6), 2088-2096.

Maladen, Perumal, Wexler & Binder-Macleod, S. A. (2007). Effects of Activation Pattern on Nonisometric Human Skeletal Muscle Performance. *Journal of Applied Physiology, Feb 1* [Epublished ahead of print].

Marsden, C. D., Meadows, J. C., Merton, P. A. (1983). Muscular wisdom" that minimizes fatigue during prolonged effort in man: peak rates of motoneuron discharge and slowing of discharge during fatigue. *Advances in Neurology, 39*, 169-211.

Meyers, B. M., Nguyen, J., & Cafarelli, E. (2001). Obtaining force-frequency curves with a single 3-second train of stimuli. *Muscle and Nerve, 24* (10), 1332-1338.

Miller, C., & Thepaut-Mathieu, C. (1993). Strength training by electrostimulation conditions for efficacy. *International Journal of Sports Medicine, 14* (1), 20-28.

Mourselas, N., & Granat, N. H. (1998). Evaluation of patterned stimulation for use in surface functional electrical stimulation systems. *Medical Engineering and Physics, 20* (5), 319-324.

Preston, D. C., Venkatesh, S., Shefner, J. M., Logigian, E. L. (1994). Submaximal stimuli activate different nerve fibers populations at different sites. *Muscle and Nerve, 17* (4), 381-385.

Rich, M. M. (2006). The control of neuromuscular transmission in health and disease. *Neuroscientist, 12* (2), 134-142.

Ratkevicius, A., & Quistorff, B. (2002). Metabolic costs of force generation for constant-frequency and catchlike-inducing electrical stimulation in human tibialis anterior muscle. *Muscle & Nerve, 25*(3), 419-426.

Russ, D. W., & Binder-Macleod, S. A. (1999) Variable-frequency trains offset low-frequency fatigue in human skeletal muscle. *Muscle and Nerve, 22* (7), 874-882.

Russ, D. W., Vandenborne, K., & Binder-Macleod, S. A. (2002). Factors in fatigue during intermittent electrical stimulation of human skeletal muscle. *Journal of Applied Physiology, 93* (2), 469-478.

Scott, W. B. & Binder-Macleod, S. A. (2003). Changing stimulation patterns improves performance during electrically elicited contractions. *Muscle and Nerve, 28,* 174-180.

Scott, W. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Switching stimulation trains improves performance of paralyzed human quadriceps muscle. *Muscle and Nerve, 31* (5), 581-588.

Scott, W. B., Lee, S. C., Johnston, T. E., Binkley, J., & Binder-Macleod, S. A. (2007). Effect of electrical stimulation pattern on the force responses of paralyzed human quadriceps muscles. *Muscle and Nerve, Jan 9* [Epublished ahead of print]

Scott Bickel, C., Slade, J. M., Van Hiel, L. R., Warren, G. L., & Dudley, G. A. (2004). Variable-frequency-train stimulation of skeletal muscle after spinal cord injury. *Journal of Rehabilitation Research and Development, 41* (1), 33-40.

Shields, R. K., Dudley-Javorski, S., & Cole, K. R. (2006). Feedback-controlled stimulation enhances human paralyzed muscle performance. Journal of Applied Physiology, 101 (5), 1312-1319.

Simpson, J. A. (1969). Terminology of electromyography. *Electroencephalography and Clinical Neurophysiology, 26,* 224-226.

Spriet, L. L., Soderlund, K., & Hultman, E. (1988). Energy cost and metabolic regulation during intermittent and continuous titanic contractions in human skeletal muscle. *Canadian Journal of Physiology & Pharmacology, 66* (2), 134-139.

Thomas, C. K., Woods, J. J., & Bigland-Ritchie, B. (1989). Impulse propagation and muscle activation in long maximal voluntary contractions. *Journal of Applied Physiology, 67* (5), 1835-1832.

Thomas, C. K., Bigland-Ritchie, B., Johansson, R. S. (1991) Force-frequency relationships of human thenar motor units. *Journal of Neurophysiology, 65*, 1509-1516.

Thomas, C. K., Griffin, L., Godfrey, S., Ribot-Ciscar, E., & Butler, J. E. (2003). Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *Journal of Neurophysiology, 89*, 202-204.

Thomas, C. K., Johansson, R. S., & Bigland-Ritchie, B. 1999 Pattern of pulses that maximize force output from single human thenar motor units. *Journal of Neurophysiology, 82* (6), 3188-3195.

Van Lunteren, F., & Sankey, C. B. (2000). Catchlike property of rat diaphragm: subsequent train frequency effects in variable-train stimulation**.** *Journal of Applied Physiology, 88*(2), 586-598.

Vigreux, B., Cnockaert J. C., & Pertuzon, E. (1980). Effects of fatigue on the series elastic component of muscle. *European Journal of Applied Physiology and Occupational Physiology, 45* (1), 11-17.

Westerblad, H., Duty, S., & Allen, D. G. (1993) Intracellular calcium concentration during low-frequency fatigue in isolated single fibers of mouse skeletal muscle. *Journal of Applied Physiology, 75* (1), 382-388.

Zijdewind, C., Bosch, W., Goessens, L., Kandou, T. W., & Kernell, D. (1990). Electromyogram and force during stimulated fatigue tests of muscles in dominant and non-dominant hands. *European Journal of Physiology and Occupational Physiology, 60* (2), 127-132.

Zory, R., Boerio, D., Jubeau, M., & Maffiuletti, N. A. (2005). Central and peripheral fatigue of the knee extensor muscles induced by electromyostimulation. *International Journal of Sports Medicine, 26,* 847-853.

# Chapter 2: The Effect of Variable Frequency Trains in Post-Stroke Hemiplegia


## ABSTRACT

The use of neuromuscular electrical stimulation (NMES) has proven effective for recovery of motor function but NMES can impart rapid fatigue and the specific parameters of stimulation that maximize force output and delay the onset of fatigue remain unclear. Variable stimulation patterns have been previously examined in healthy and spinal injured populations, but little evidence exists for the effectiveness of variable stimulation patterns administered to chronic stroke (CVA) survivors. We administered three different variable stimulation patterns to the thenar muscles of individuals chronically paralyzed by stroke and an age-matched able-bodied group: 1) a 20 Hz pattern, 2) an increasing pattern of 20-40 Hz, and 3) a doublet pattern. In the able-bodied, force time integrals (FTIs) were 0.829 ± 0.01, 1.06 ± 0.01, and 1.41 ± 0.01 kN•s for the three patterns respectively; in the CVA participants, FTI was 0.639 ± 0.01, 0.796 ± 0.01 and 0.778 ± 0.01 kN•s respectively. In the able-bodied, higher average forces (7.84 ± 1.25 N) were reached during doublet stimulation. In the CVA participants, an increasing frequency pattern produced the highest average force (4.54 ± 0.96 N). For post-stroke individuals, the doublet pattern had a minimal effect overall, and for several, this pattern lessened what little force output was present. Voluntary forces in the CVA condition were 18.20 ± 3.78% lower and evoked forces were 20.86 ± 2.31% lower than forces in the able-bodied group. Able-bodied and paralyzed tissue show differences in response to variable stimulation patterns, therefore consideration of stimulation parameters to maximize force output is essential.

## INTRODUCTION

Application of neuromuscular electrical stimulation (NMES) to paralyzed muscle is a commonly-used intervention in clinical settings and the related scientific literature has shown NMES to be effective in facilitating the return of motor control following neurological insult. Several studies agree that beneficial outcomes can be obtained when electrical stimulation has been used following cerebral vascular accident (CVA/stroke) for gait training (Robbins, Houghton, Woodbury, & Brown, 2006; Yan & Hui-Chan, 2005; Tong, Ng, Li, & So, 2006), muscle re-education (Cauraugh, Light, Kim, Thigpen, & Behrman, 2000; Powell, Pandyan, Granat, Cameron, & Stolt, 1999), functional activity performance (Chae et al., 1998; Berner, Lif Kimchi, Spokoiny, & Finkeltov, 2004; Gritsenko & Prochazka 2004), spasticity reduction (Ring & Rosenthal, 2005; Chen et al., 2005), pain control (Chantraine, Baribeault, Uebelhart, & Gremion, 1999; Chae Yu & Walker, 2001; Renzenbrink & Ijzerman, 2004), motor skill retraining (Wang, Yang, Tsai, Wang, & Chan, 2002; Kraft, Fitts & Hammond, 1992), as well as restoration of sensory awareness (Eskes, Butler, McDonald, Harrison, & Phillips, 2003; Sullivan & Hedman 2004; Peurala, Pikanene, Sivenius, & Taarka, 2002) and improvement in shoulder subluxation (Aoyagi & Tsubahara, 2004, Chae et al., 2001). NMES programs that elicit functional movement patterns have also been incorporated into several neuroprosthetic devices (Hendricks, Ijzerman, deKroon, Groen, & Zilvold, 2001; Popovic et al., 1999) or implanted systems (Hobby, Taylor, & Esnouf, 2001; Chae et al., 2001) that patients now have access to for functional or retraining purposes.

Where there is less agreement is in the specific parameters of NMES (i.e., frequency, pulse duration, intensity, duty cycle, application schedule, etc.) that should be used to achieve optimal clinical outcomes. Recent evidence suggests that patterns of

NMES that closely replicate the variable physiological firing patterns that occur in human motor units during voluntary muscle activity may be better suited for restoring motor control than constant-frequency protocols (Scott, Lee, Johnston, Binkley, & Binder-Macleod, 2007). Single motor unit firing rates typically decline and then increase, as observed in submaximal contractions (Adam & De Luca, 2005; Garland, Griffin, & Ivanova, 1997; Dorfman, Howard, & McGill, 1990;); therefore, higher frequencies are required to maintain force output once muscle becomes fatigued (Russ, Vandenborne, & Binder-Macleod, 2002; Meyers, Nguyen, & Cafarelli, 2001; Binder-McLeod & McDermond 1992). Stimulation patterns that progressively increase in frequency also have been shown to extend force output (Kebaetse, Lee, Johnston, & Binder-Macleod, 2005). Additionally, NMES programs that use more physiological frequencies (e.g., 10-40 Hz) may result in more efficient force output and less fatigue (Kesar & Binder-Macleod, 2006; Jones, Bigland-Ritchie, & Edwards, 1979).

Variable frequency trains (VFTs) of electrical stimulation have been used extensively to observe the force response when applied to able-bodied and paralyzed muscle. In able-bodied muscle, the implementation of VFTs has improved muscle excursion (Maladen, Perumal, Wexler, & Binder-Macleod, 2007; Kebaetse, Turner, & Binder-Macleod, 2002), enhanced force-time integrals (Allman, Cheng, & Rice, 2004; Ratkevius & Quistorff, 2002; Binder-Macleod & Scott, 2001) and produced greater torque (Bickel, Slade, Warren, & Dudley, 2003; Slade, Bickel, Warren, & Dudley, 2003) with robust consistency when compared to constant frequency trains. Far less investigation has focused on paralyzed tissue, and no study to date has examined the outcomes of VFTs of stimulation used on muscle paralyzed by stroke. Variable frequency trains have enhanced force output compared to constant frequency trains when tested in quadriceps paralyzed by spinal injury (SI) during isometric (Scott et al., 2007) and non-isometric tasks (Kebaetse et al., 2005). The SI-paralyzed soleus muscle also showed enhanced torque output when an increasing frequency train was implemented at the onset of fatigue using a feedback-controlled mechanism (Shields, 2006). Using a variable stimulation pattern was likewise successful in increasing force in healthy as well as SI-paralyzed quadriceps (Karu, Durfee, & Barzilai, 1995). Others have indicated that the effect of VFTs is minor and that enhancement of force is seen only when overall low frequencies are used (~20 Hz) (Mourselas & Granat, 1998); however, this was refuted in recent work that showed the effect present when a 50 Hz frequency was used (Slade et al., 2003). Evidence remains controversial as to whether the benefits of VFTs are similar in able-bodied musculature when compared to paralyzed musculature. Scott Bickel, Slade, Van Hiel, Warren, & Dudley (2004) found that when VFTs were applied to healthy and SI-injured quadriceps, torque output was enhanced in the fatigued healthy muscle to a greater extent than in the fatigued SI-paralyzed muscle. In contrast, Griffin, Godfrey and Thomas (2002) saw no difference in force decline between populations when several VFTs using both high and low frequencies were administered to healthy and SI-paralyzed thenar muscle. Inconsistencies remain and the effect of VFTs in paralyzed and healthy muscle requires further investigation.

Other naturally-occurring motor unit firing patterns, such as doublets (two electrical pulses separated by less than 20ms) frequently have been incorporated into investigational NMES patterns. Most have tested brief trains of stimulation during non-fatiguing contractions and found that the trains with doublets produce significantly more force than trains without doublets (Van Lunteren and Sankey 2000; Binder-Macleod and Scott, 2001; Griffin et al. 2002; Duchateau and Hainaut 1986; Macefield, Fuglevand, & Bigland-Ritchie, 1996). The force enhancement effect with doublets has been shown to be even greater following fatigue (Scott et al., 2007; Scott et al., 2005; Bigland-Ritchie, 2

Zijdewind, & Thomas 2000; Ratkevicius and Quistorff 2002) and in paralyzed versus non paralyzed muscle (Griffin et al., 2002). Doublet trains that follow single pulse trains have also extended force output effectively (Scott & Binder-Macleod, 2003). This investigation will examine the fatigue effects of three different neuromuscular electrical stimulation programs that incorporate variable patterns applied to the thenar muscles of both able-bodied and post-stroke hemiplegic individuals: 1) a 20 Hz single pulse train, (herein after referred to as 20 Hz train) 2) a progressively increasing 20 Hz to 40 Hz pulse train, (20-40 Hz) and 3) a 20 Hz single pulse train that switches to a 20 Hz doublet pulse train (doublet train).

A stimulation frequency of 40 Hz was selected because it creates a contraction force close to a maximum voluntary contraction and is typical of maximum average motor unit discharge rates (Keeton & Binder-Macleod, 2006). A 20 Hz stimulation level was selected because this frequency evokes a moderate muscular contraction and is often used in clinical regimens (Baker, Wederich, McNeal, Newsam, & Waters, 2000). Lower frequencies have also been shown to fatigue paralyzed muscle much less than higher frequencies (Mourselas & Granat, 1998). In previous work from our laboratory, 3-minute continuous trains that increased (20-40 Hz) or decreased (40-20 Hz) frequency at the *onset* of stimulation showed no differences in overall FTI when compared to a constant 20 Hz pattern (Griffin, Jun, Covington, & Doucet, 2006). This suggests that variable frequency trains may work optimally when implemented at a point in which the muscle has already become fatigued. Similar work has shown a moderate degree of fatigue (approximately 25% decrease of initial force output value) to occur in thenar muscle at the 60-90s time period of stimulation (Thomas, Griffin, Godfrey, Ribot-Ciscar, & Butler, 2003); likewise, our data indicated decreases in force of 31.20 ± 2.52 % at the 90s mark. We chose to switch patterns to an increasing frequency or doublet pattern at this time interval. Furthermore, previous work has indicated that combining different frequency trains (Scott & Binder-Macleod, 2003) or following a low-frequency train with a higher frequency train (Kebaetse & Binder-Macleod, 2004) has the potential to significantly augment force output.

We also chose to examine the effects of "low-frequency fatigue" in the hemiplegic population, because this also has not been previously studied. Low-frequency fatigue (LFF) was first described by Edwards, Hill, Jones, & Merton (1977) and has been often observed by others (Russ, Vandenborne & Binder-Macleod, 2002; Westerblad & Allen, 2002). LFF is a condition in which significant force loss is seen during stimulation at lower frequencies in fatigued muscle. This can persist for several hours to days and is not typically apparent during higher frequencies of post-fatigue stimulation (for review, see Keeton & Binder-Macleod, 2006).

We hypothesized that trains that increase in frequency and trains that contain doublets will demonstrate greater force output over time and will delay the onset of fatigue when compared to constant frequency patterns in both populations. We also predicted that, due to overall lower forces typically produced in paralyzed muscle, the effect of the variable stimulation patterns on force output during a fatigue task will be greater in paralyzed than in the age-matched healthy participants.

**METHODS**

## Participants

A total of twenty participants were recruited for this study: ten individuals who sustained a stroke with resultant upper extremity hemiplegia at least one year prior (avg.

age, 63.80 ± 12.69 years; 8 males, 2 females) and ten age-matched able-bodied adults (avg. age, 63.60 ± 12.88 years; 6 males, 4 females).

Stroke survivors were recruited from the Austin, TX, vicinity through a local newspaper advertisement over a 12-month period. Participants were selected if the following criteria were met: 1) status post stroke onset of at least 1 year prior to start of study involvement; 2) full discharge from any inpatient, outpatient, or home health therapies; 3) in general good health without significant cognitive impairment; 4) able to maintain forearm pronation, full digit extension, and actively adduct the thumb at least 30° for positioning and testing in the experimental apparatus; 5) able to comprehend objectives of study and follow study-related directions. The exclusion criteria for the post-stroke participants were: presence of extensive spasticity or flaccidity in the affected upper extremity, contraindication for the application of electrical stimulation (pacemaker, skin lesions at application site, etc.), confusion or disorientation, presence of pain syndromes of the upper extremity, or implanted surgical hardware in the hand or forearms. Age-matched able-bodied participants were selected from the University of Texas and Austin communities.

All individuals were in general good health with no physical limitation or significant medical history of neuromuscular or cardiac disorder. All participants underwent an orientation session and signed consent forms prior to any testing. A medical clearance form was signed by physicians who were familiar with the medical history of the post-stroke participants to insure that experimental activities would be safely tolerated. Participation was voluntary and participants were free to withdraw at any time during the study. All procedures were in compliance with and approved by the University of Texas Institutional Review Board policies on Human Subject Research.

**Experimental Setup**

The experimental apparatus and setup has been described previously (Griffin et al., 2006). Participants were seated in a high-back chair with their right forearm supinated and resting on a tabletop. The shoulder and upper arm were positioned parallel with the trunk and the elbow was positioned at 90º. A custom-designed forearm apparatus made of thermoplastic material (Smith & Nephew, Rolyan, USA) immobilized the forearm and maintained the extremity in a position of supination. The forearm apparatus was attached to a ½" thick sheet of laminated coreboard that was bolted to the laboratory table. Straps secured the forearm at the wrist and forearm midpoint; the upper arm was secured with a strap positioned slightly medial to the elbow that attached to the upper back portion of the chair. The hand was stabilized with therapeutic putty placed underneath, securing the dorsum; putty was placed on the volar surface as well, extending slightly below the metacarpal-phalangeal (MCP) joints to mid-palm. A thermoplastic plate was positioned on the putty over the digits and a strap helped to secure the interphalangeal (IP) joints and the MCP joints in extension. The thumb was extended and abducted and positioned against the force transducer. The custom-designed force transducer device (Mechanical Engineering Shop, University of Texas at Austin) consisted of a mobile, rotating, height-adjustable horizontal arm made of two narrow aluminum surfaces: a vertical surface that measured thumb adduction force (x), and a horizontal surface that measured any thumb extension force present (y). A moderate stretch into abduction was placed on the thumb to position it against the transducer surface. The contact area spanned from the thumb tip to midway between the IP and MCP joint (Figure 2.1). The force output as a result of stimulation emanated directly from the IP joint onto the transducer surfaces. The resultant force, $R = \sqrt{x^2 + y^2}$, was calculated, displayed on the computer monitor, and recorded using commercially-available software (Spike 2, Version 5.14, Cambridge Electronics Design).

A stimulating electrode with the anode and cathode 2 cm apart was placed over the median nerve, slightly medial to the wrist and secured with a velcro band and tape after optimal placement was obtained. Electrical impulses of 50 µs pulse duration were delivered through the stimulating electrode from a constant current stimulator (Digitimer, Ltd., Model DS7A, Welwyn Springs, UK) using custom-written scripts constructed through the Spike 2 software. The force output signal was amplified by 100 sampled at 1000 Hz and low-pass filtered at 1kHz (Bridge 8 Amplifier System, Model 74030, World Precision Instruments). The electromyographic (EMG) signal was recorded through two adhesive pre-gelled Ag/AgCl• bipolar surface electrodes 5mm in diameter (Danlee

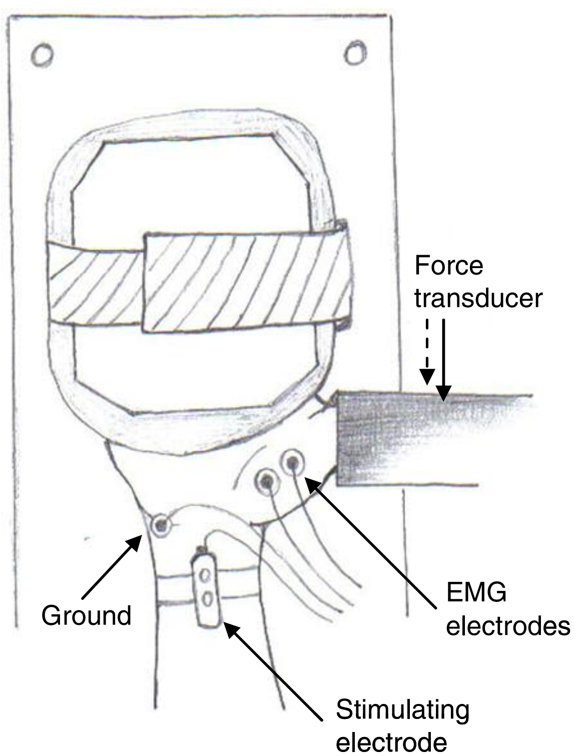


Figure 2.1. Experimental set-up and upper extremity positioned in place for testing.

Medical Products, Inc. USA). The active electrode was placed over the thenar eminence slightly medial to the MCP joint of the thumb and the reference electrode approximately 1cm medial to the active electrode. The third (ground) electrode was placed over the pisiform bone. EMG was amplified by 100, high-pass filtered above 8 Hz, (Coulbourn Instruments Isolated Bioamplifier with Bandpass Filter, Model V75-04) sampled at 2000 Hz, and digitally converted (Micro 1401 mkII 500kHz 16-bit Analog-Digital Converter with ADC 12 Expansion, Cambridge Electronics Design).

**Experimental Protocol**

Isometric force output during evoked thumb adduction was investigated using three different types of electrical stimulation trains. All fatigue protocols were composed of intermittent bursts of 300 ms "on" time and 700 ms "off" time based on the Burke experimental protocol used frequently in neuromuscular electrical stimulation research (Burke et al., 1973). An intermittent stimulation train remains on for 300 ms and off for 700 ms and elicits only six of the described pulses for a 20 Hz pattern. Three (3) different fatigue tests consisting of a combination of stimulation trains were administered at submaximal stimulation levels during three different testing sessions. Each session was separated by at least 48 hours to recover from possible effects of low frequency fatigue.

Fatigue Test 1 was the baseline measure and consisted of a 3-minute intermittent 20 Hz train. Fatigue Test 2 was the gradually increasing stimulation train that consisted of a 3-minute intermittent train that began at 20 Hz, and midway through the protocol (90 seconds), began gradually increasing in frequency from 20 Hz to 40 Hz such that 40 Hz was the terminal frequency reached at 180 seconds. Fatigue Test 3, the doublet train, similarly began at 20 Hz, and midway through the protocol (90 seconds) the pattern changed to a doublet pattern (6 doublets administered during the 300 ms "on" time with interpulse intervals of 5ms) that continued to the end of the train. Figure 2.2 graphically displays the three trains used in the three fatigue tests. Both able-bodied and post-stroke participants received the protocol described below:

Prior to each fatigue test, three 3-second maximal voluntary contractions (MVCs) of thumb adduction were performed. An average was taken from the MVCs and was used to determine stimulation intensity. Single 1 Hz pulses were delivered with a pulse width of 50 μs. These pulses were given at various stimulator placements to elicit the maximum compound muscle action potential (M-wave). The M-wave amplitude and twitch were monitored during these pulses. Intensity was progressively increased by 1 μA to obtain maximal M-wave and twitch. Thereafter, intensity was reduced to a submaximal level. Intermittent 1-second 20 Hz trains were delivered until the force output produced 20% of the thumb adduction MVC force value. This intensity was used for the subsequent fatigue test.

Once appropriate intensity was determined, the fatigue test began. Five supramaximal 1 Hz pulses of 50 μs were administered to insure optimal stimulator placement and maximal M-wave. Intensity was then reduced to the appropriate level. This was followed by administration of the 4-second constant 20 Hz train. Our aim was to obtain similar values for the force elicited by this 4s train from session to session, maximizing reliability of stimulator placement and positioning. Three maximal voluntary contractions of thumb adduction (MVCs) lasting approximately 3 seconds each were then performed. This was followed by the delivery of 5 random, constant frequency, 4-second trains of 10, 20, 30, and 40 Hz and a 2-second train of 50 Hz. Each of these 4-second trains was separated by 3 seconds. These data were collected to monitor force at various frequency levels before and after fatigue. Additionally, we wanted to determine if significant differences were present during low-frequency post-fatigue trains as compared to higher frequency post-fatigue trains to examine possible LFF effects. The 3-minute fatiguing stimulation train then followed. Ten seconds elapsed between the five 1 Hz pulses, the 4-second 20 Hz train, the three MVCs, the five trains of varying frequencies, and before the fatiguing train began. One of the three different fatiguing stimulation trains was administered at each session. At the completion of the fatiguing stimulation train, 3 seconds rest elapsed, then the 5 constant frequency trains were again delivered, followed by another 3 seconds rest, then repetition of the 3 MVCs. The test commenced with delivery of intermittent 1 Hz 50 μs pulses to monitor M-wave changes and recovery. See schematic of the testing protocol (Figure 2.3).

Each of the three experimental sessions followed the same protocol and was identical except for the fatiguing train administered. Participants were stimulated with only one fatigue test per visit (Fatigue Test 1, constant 20 Hz train; Fatigue Test 2, gradually increasing frequency train; or Fatigue Test 3, doublet train) and the order was randomized across participants.

**Data Analysis**

Forces at 10s intervals were measured for every stimulation pattern administered (20 Hz, 20-40 Hz and doublet). The three patterns were compared to assess which pattern maximized force output over time. Overall force-time integrals (FTIs), the total area under the fatiguing stimulation train force trace, were computed from the interval measures. FTIs were calculated as kN•s and are reflective of the total force production during the given fatigue test. Overall peak forces (the maximum force elicited during the fatiguing stimulation pattern as measured from baseline to peak) were also obtained.

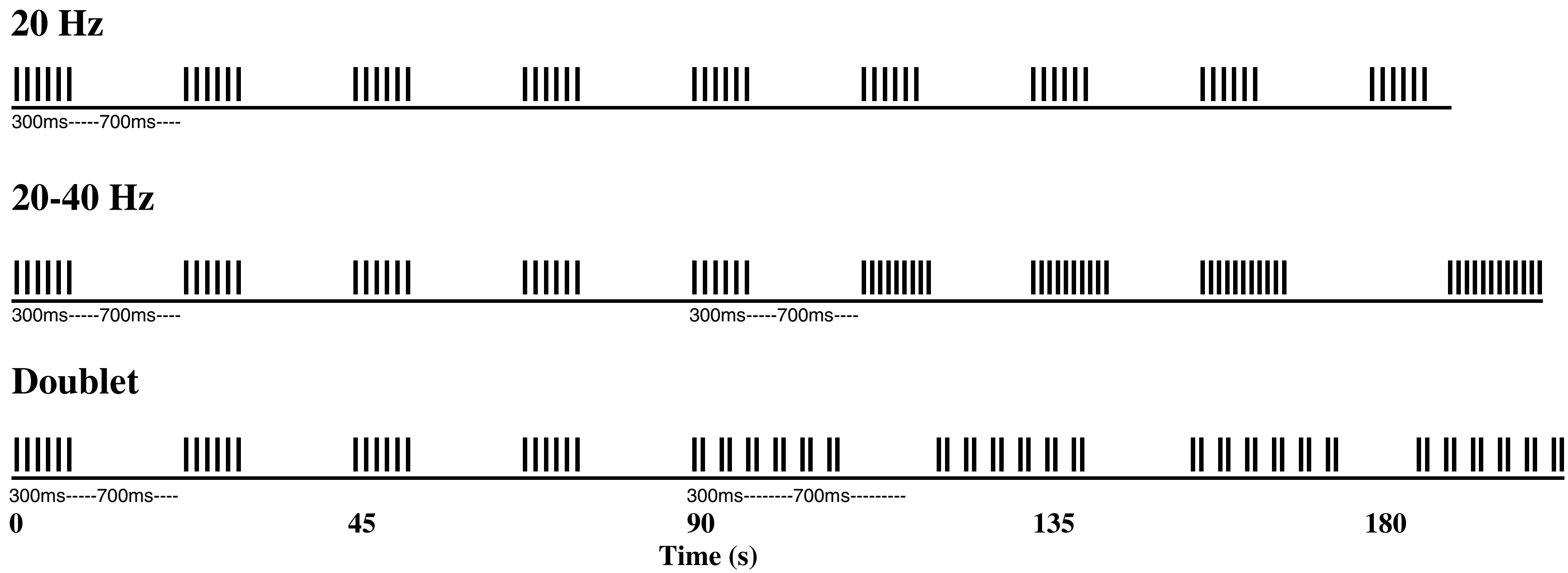


Figure 2.2. **20 Hz**:Graphic representation of pulses at second 1, second 90, and second 180 during the 3-minute, 20 Hz intermittent stimulation train (Fatigue Test 1). Using the Burke (1973) protocol, stimulation is on for 300ms, and off for 700 ms during each second of stimulation. **20-40 Hz**: Graphic representation of change in pulse pattern which begins after second 90. Increases in pulses are shown at seconds 105, 120, 135, 150, and 175 (Fatigue Test 2). **Doublets**: Graphic representation of doublet pulses that began at second 90, continuing through second 180. Doublet pulses were of 1ms duration separated by a 5ms interval (Fatigue Test 3)

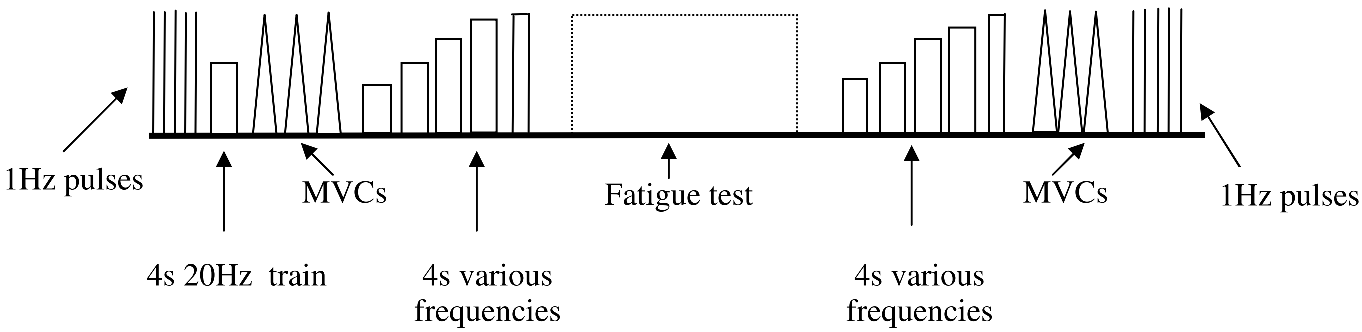


Figure 2.3: Graphic representation of study protocol. The 1Hz pulses, 4s 20Hz train, MVCs and 5 varying frequencies prior to the fatiguing protocol were separated by 10s each. After the fatiguing protocol, 3s elapsed between fatigue protocol, 5 varying frequencies, MVCs, and final 1Hz pulses.

Maximum evoked forces from each of the five 4-second frequency trains of thumb adduction were measured before and after each fatiguing train. Maximal voluntary contractions (MVCs) performed before and after the fatiguing stimulation train were measured and compared. Peak-to-peak M-wave amplitudes (calculated as a percentage of maximum) were measured at 10s intervals throughout each fatigue test.

**Statistical Analysis**

Force at 10s intervals for each of the three experimental protocols was one of the dependent variables measured. These were compared using a two-way repeated measures analysis of variance (ANOVA) with pattern (20 Hz, 20-40 Hz and doublet) and condition (able-bodied vs. CVA) as the independent variables. Tukey tests were used for pairwise post-hoc comparisons.

MVCs were another dependent measure. Declines from pre-stimulation to post-stimulation were calculated. These values were analyzed separate from evoked stimulation due to being performed voluntarily. MVCs performed before and after the fatiguing stimulation train were compared with a 3 X 2 X 2 repeated measures ANOVA using pattern (20 Hz, 20-40 Hz, or doublet), condition (able-bodied or post-stroke), and time (pre- or post-fatiguing stimulation pattern) with post hoc Bonferonni corrections.

The maximal forces obtained for each of the five various frequency trains (10, 20, 30, 40, and 50 Hz) performed before and after the fatiguing stimulation train were our third dependent measure. Pattern (20 Hz, 20-40 Hz, doublet) and time (pre-fatigue, post-fatigue) were the dependent variables and were compared between the two conditions. . This determined the effects of pattern, condition, and time on evoked contractions of thumb adduction at the five various frequencies and would provide any evidence of low-frequency fatigue. A multivariate analysis of variance (MANOVA) was used for this comparison, with univariate ANOVAs and Bonferroni corrections for post hoc analysis. M-wave amplitudes were collected before and after testing and also compared using a 3 X 2 X 2 repeated measures ANOVA. This analysis was used to ensure that stimulator placement remained stable throughout testing.

An alpha level of 0.05 was used for all statistical comparisons and significance accepted when P • 0.05. All data are presented as mean ± standard deviation throughout the text and mean ± standard error for the tables and figures.

**RESULTS**

## Day to Day Repeatability

There was no significant difference in the MVC forces between experiment days. A one-way repeated measures ANOVA showed that MVCs were similar for participants across the 3 days tested. Average MVC forces collected before the 20 Hz, 20-40 Hz and doublet tests were 65.67 ± 6.74 N, 68.44 ± 6.88 N, and 67.80 ± 7.25 N for the able-bodied participants and 55.32 ± 9.34 N, 56.95 ± 9.08 N, and 52.89 ± 8.50 N for the CVA participants. On average, MVC forces for the CVA participants were 18.20 ± 3.78% lower than forces in the able-bodied group.

Additionally, a 4-second 20 Hz stimulation train was administered at the onset of every test and compared across sessions for additional reliability using a one-way repeated measures ANOVA for each condition. No significant differences were found in evoked forces across protocols: Average evoked forces for the 20 Hz, 20-40 Hz, and doublet protocols, respectively, were 11.43 ± 5.11 N, 11.21 ± 3.64 N, and 11.88 ± 5.15 N for the able-bodied; 8.76 ± 3.40 N, 9.06 ± 3.29 N, and 9.50 ± 2.54 N for the post-stroke individuals. Evoked forces in the CVA participants were 20.86 ± 2.31% lower than evoked forces in the able-bodied.

**Force and Force-Time Integrals**

Average forces for the able-bodied were 4.72 ± 0.87 N for the 20 Hz; 5.98 ± 0.12 N for the 20-40 Hz; and 7.84 ± 1.25 N for the doublet pattern. Average forces for the CVA participants were 3.69 ± 1.52 N for the 20 Hz; 4.54 ± 0.96 N for the 20-40 Hz; and 4.46 ± 1.38 N for the doublet pattern. Peak forces for the able-bodied were as follows: 20 Hz: 6.80 ± 3.28 N; 20-40 Hz 7.00 ± 2.78 N; and doublet, 10.51 ± 4.44 N. Peak forces for the post-stroke participants were as follows: 20 Hz: 6.19 ± 5.45 N; 20-40 Hz 6.75 ± 4.36, and doublet, 6.94 ± 5.07 N. For the able-bodied, peak forces were reached at the onset of the 20 and 20-40 Hz pattern; however, the peak force during the doublet stimulation occurred at the onset of the doublet pattern (90 second mark). All peak forces occurred at the onset of stimulation for the CVA participants. Figure 2.4 shows the average forces evoked from stimulation at each of the 10s intervals over the three fatiguing stimulation patterns for each of the two conditions.

Force time integrals (FTIs) showed significant overall differences between pattern and conditions (P = <0.001 for both). See Figure 2.5. In the able-bodied, force time integrals (FTIs) were 0.829 ± 0.01 for the 20 Hz pattern, 1.07 ± 0.01 for the 20-40 Hz, and 1.41 ± 0.01 kN•s for the doublet pattern. Pairwise comparisons indicated that for the able-bodied, all three pattern interactions (20 Hz X 20-40 Hz; 20 Hz X doublet; 20-40 Hz

X doublet) were significantly different (P = <0.001 for all). In the able-bodied, the doublet pattern produced a significantly higher FTI.

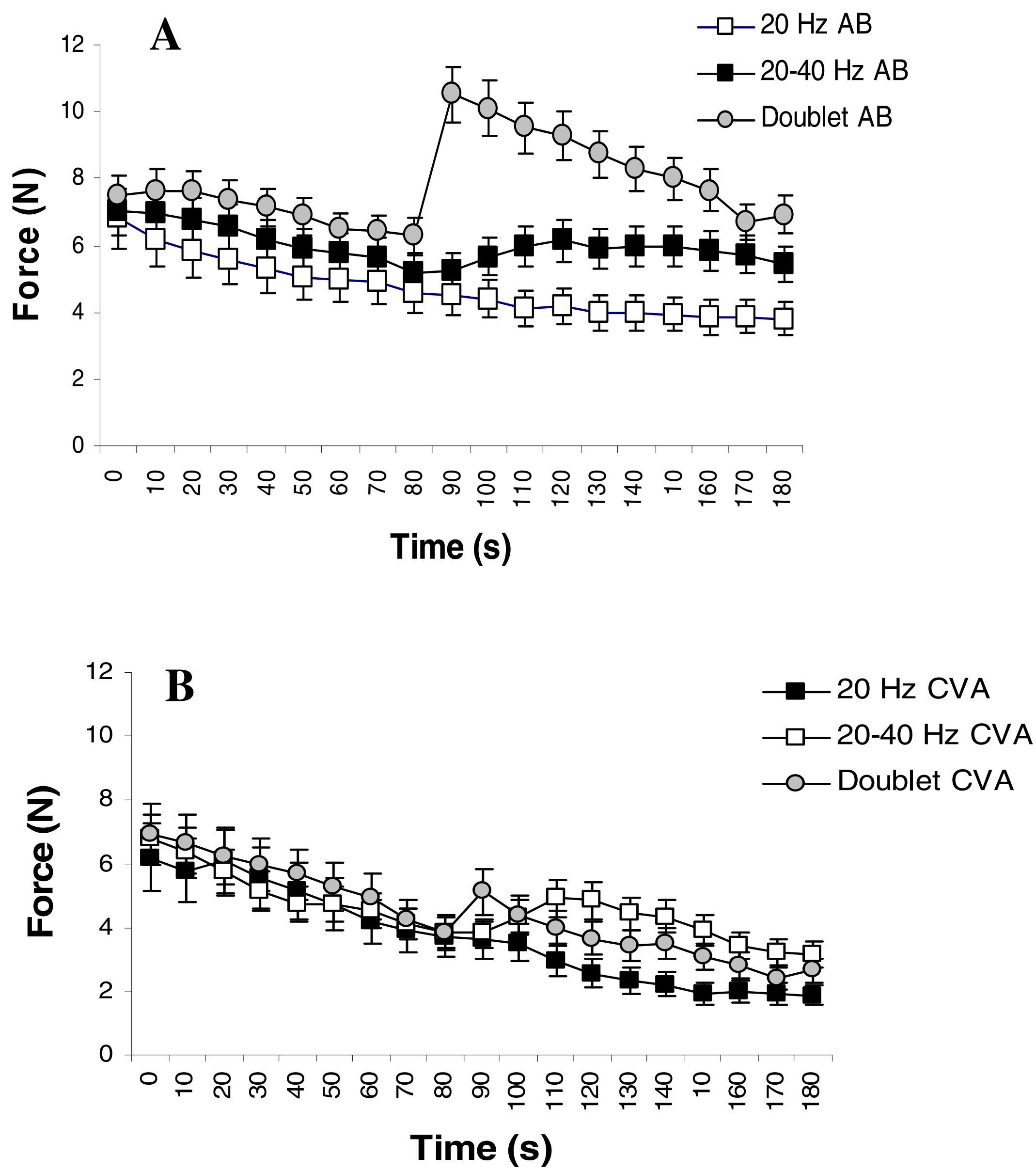


Figure 2.4.**A.** Average forces recorded at 10s intervals during the three fatiguing stimulation patterns in the able-bodied. **B**. Average forces recorded at 10s intervals during the three fatiguing stimulation patterns in the post-stroke participants.

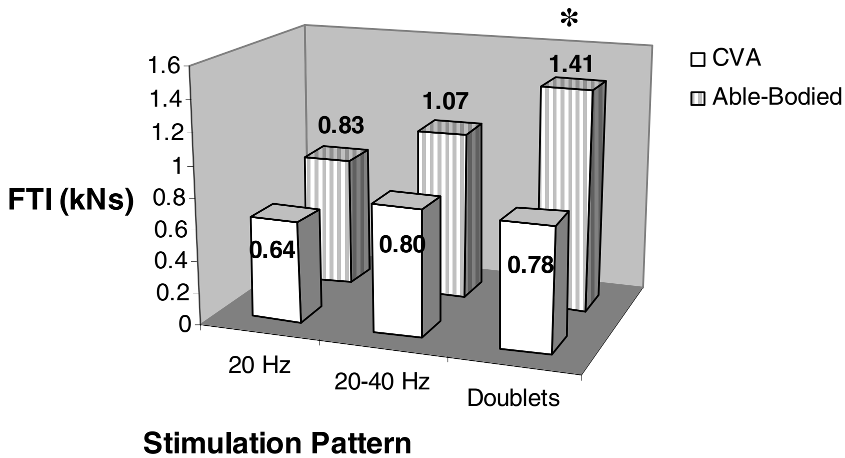


Figure 2.5. Force-time integrals in both populations for the three stimulation patterns

In the CVA participants, FTI was 0.639 ± 0.01, 0.796 ± 0.01 and 0.778 ± 0.01 kN•s respectively. For those with stroke, the 20 Hz X 20-40 Hz (P= 0.002) and the doublet X 20 Hz (P= <0.007) showed significant differences, with the 20 Hz pattern producing a significantly lower FTI than the other two patterns. There was no significant difference in the doublet X 20-40 Hz pattern FTI in the post-stroke condition.

The doublet pattern in the able-bodied increased the force output immediately when applied at 90s (66.91 ± 0.25% above 80s value). Figure 2.6 shows the raw force data for all the participants. The same pattern had less effect in the CVA participants, increasing force only 33.49 ± 0.66% above preceding value. Although all three patterns in the able-bodied maintained force relatively well for the first 90s (average decrease from initial force: 24.95 ± 8.35%) none of the patterns applied to the stroke participants maintained force through the first 90s and force loss occurred immediately upon onset of stimulation (average drop in force: 42.68 ± 2.08% from initial).

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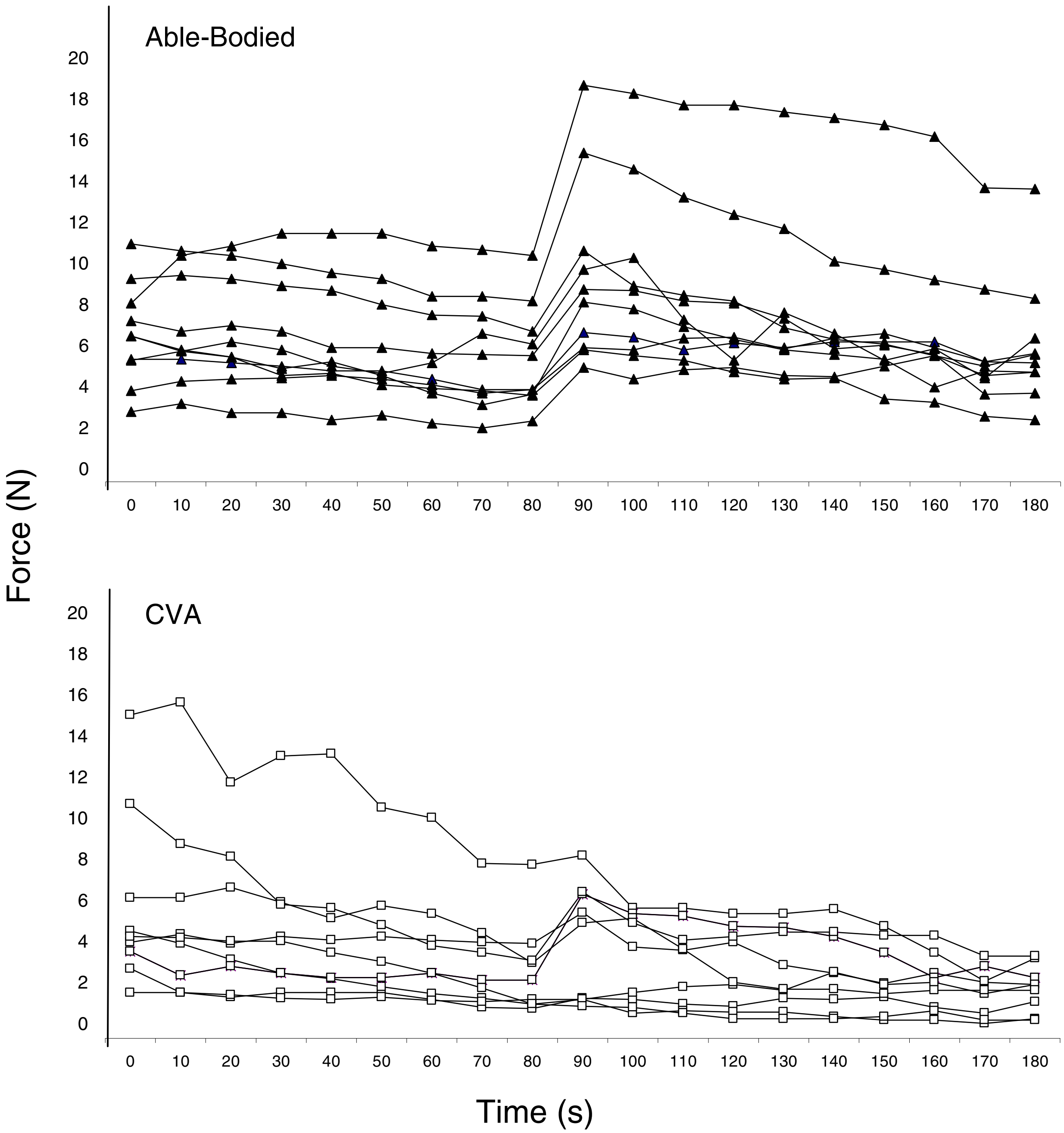



Figure 2.6. Raw data indicating force levels at 10s time increments during the doublet stimulation protocol for able-bodied (top graph) and post-stroke participants (bottom graph). A notable increase in force is evident at second 90 s mark for all the able-bodied; increases at 90s are only present in half of the post-stroke participants.

**Maximal Voluntary Contractions**

Maximal voluntary contractions (MVCs) were performed before and after each of the fatiguing stimulation patterns. In the able-bodied participants, MVCs showed an average drop from pre-stimulation to post-stimulation of 9.25 ± 3.80% MVC for the 20 Hz pattern, 10.56 ± 2.92% MVC for the 20-40 Hz pattern, and 12.47 ± 3.08% MVC for the doublet pattern. Pre-post MVC changes yielded decreases of 4.08 ± 4.00% MVC for the 20 Hz pattern, 7.89 ± 3.87% MVC for the 20-40 Hz pattern, and 17.31 ± 3.62% MVC for the doublet pattern in the post-stroke individuals. Overall differences were seen across patterns (P=0.035) without any significant pairwise interactions; time was also a significant factor overall (P=<0.001).

**Force-Frequency Distributions**

Averaged force frequency data from the 10, 20, 30, 40 and 50 Hz trains for each pattern in the two conditions can be seen in Figure 2.7. Able-bodied participants showed higher average forces when compared to post-stroke participants: 10 Hz, 7.15 ± 0.85 vs. 7.08 ± 0.74 N; 20 Hz, 12.05 ± 1.93 vs. 10.58 ± 0.76 N; 30 Hz, 14.99 ± 2.39 vs. 12.59 ± 0.94 N; 40 Hz, 16.12 ± 2.70 vs. 12.99 ± 1.21 N; and 50 Hz, 16.65 ± 3.00 vs. 13.32 ± 1.35 N.

Statistical analysis of percentage decreases in the five evoked forces before and after application of the fatiguing stimulation pattern indicated a significant overall effect of frequency (P<0.001), pattern (P=0.029) and time (P <0.001). For the able-bodied, pairwise post-hoc comparisons indicated that force loss during 10 Hz trains were significant for all three patterns (P=0.01, 0.002 and 0.001 for 20, 20-40 and doublet trains, respectively). In the post-stroke condition, significant force loss was seen at 10 Hz (P=0.002) and 20 Hz (P=0.02) trains in the increasing frequency pattern and at the 10 Hz train in the doublet pattern (P=0.04).. No significant differences were found between conditions. Force-frequency distributions are presented in Figure 2.8 and 2.9.

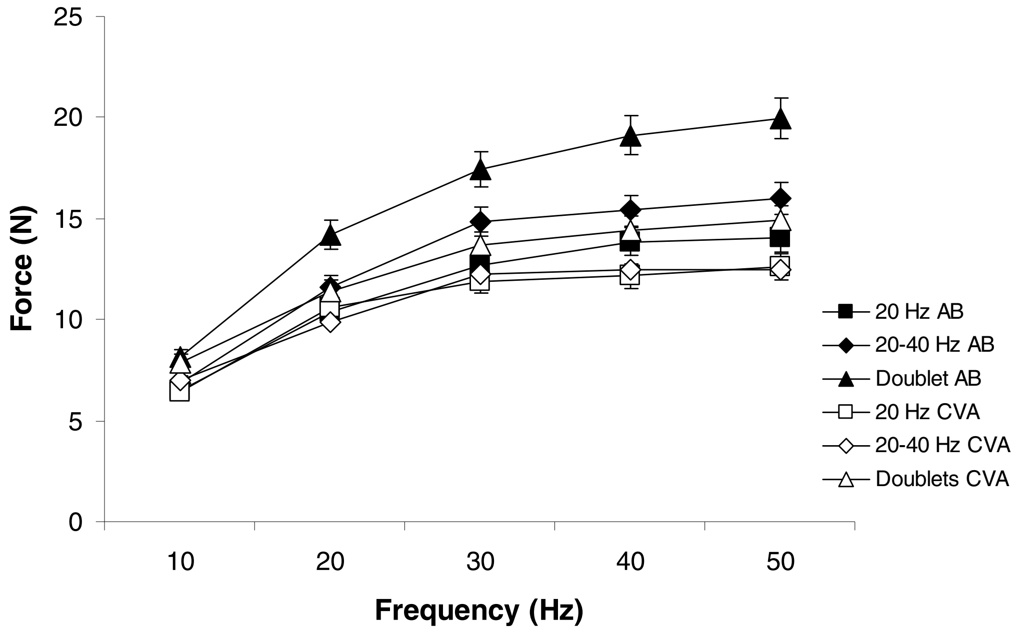



Figure 2.7.Average forces recorded during the 4s constant frequency trains of 10, 20, 30, 40, and 50 Hz for all stimulation patterns at both intensities.

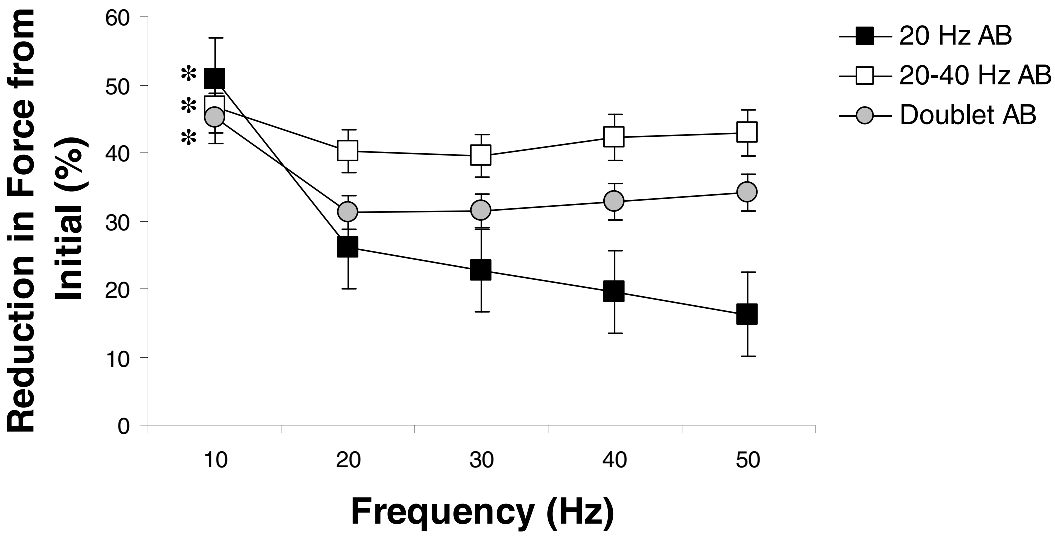



Figure 2.8. Force vs. frequency curves for the three stimulation patterns in the able-bodied. Force loss at the 10 Hz train was significantly greater (P =0.001) in all patterns.

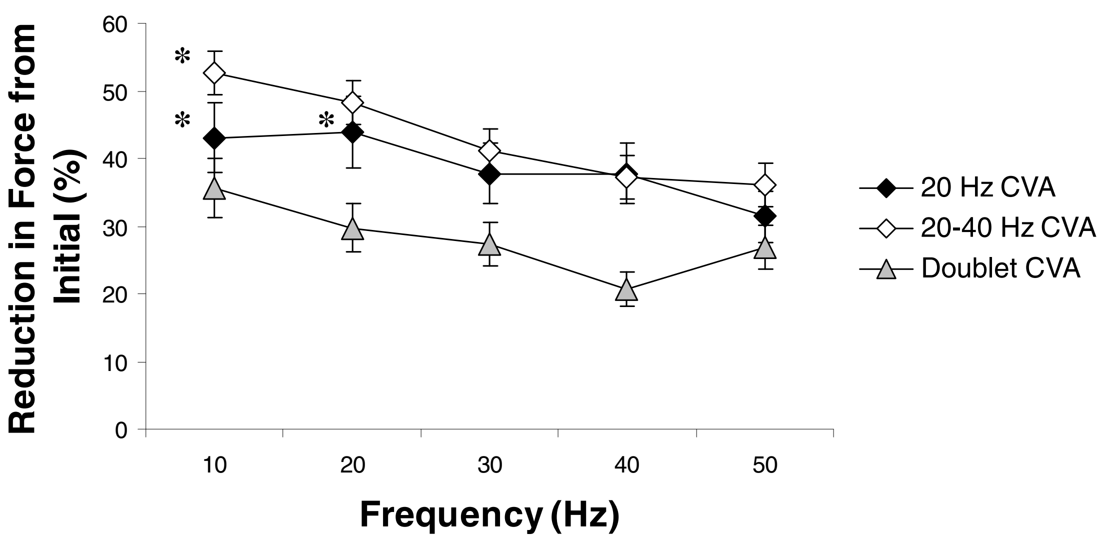



Figure 2.9. Force vs. frequency curves for the three stimulation patterns in the post-stroke participants. Significant differences were present at the 10 Hz train (P=0.04) in the doublet pattern and at the 10 Hz train (P=0.002) and 20 Hz train (P=0.02) in the 20-40 Hz pattern.

**M-Wave Stability**

M-wave amplitudes were measured prior to testing and at the completion of all tests to ensure stability of the stimulating electrode. Average m-wave values before and after stimulation for the able-bodied condition was as follows: 20 Hz, 0.68 ± 0.37 pre, 0.65 ± 0.32 mV post; 20-40 Hz, 0.69 ± 0.38 pre, 0.67 ± 0.37 mV post; doublet, 0.89 ± 0.53 pre, 0.82 ± 0.44 mV post. Average m-wave values before and after stimulation for the post-stroke participants was 0.56 ± 0.32 pre, 0.53 ± 0.34 mV post for the 20 Hz pattern, 0.67 ± 0.36 pre, 0.66 ± 0.38 mV post for the 20-40 Hz pattern, and 0.68 ± 0.49 pre, 0.70 ± 0.50 post for the doublet pattern. The 3 X 2 X 2 repeated measures ANOVA indicated no significant overall differences in pre-post values, validating consistency in electrode placement and stability. Additionally, no significant differences were present between patterns or conditions. Submaximal to maximal m-wave ratios were calculated and indicated that submaximal to maximal m-wave amplitudes ranged approximately 80% for most patterns: For the able bodied, m-wave ratios were as follows: 20 Hz, 77.27 ± 8.04%; 20-40 Hz, 80.68 ± 5.96%; doublet, 77.11 ± 1.44%. In the post-stroke participants, m-wave ratios were 78.21 ± 10.53% for the 20 Hz pattern, 78.90 ± 11.63 for the 20-40 Hz, and 54.61 ± 23.46% for the doublet pattern.

## DISCUSSION

Our study investigated differences in three submaximal stimulation patterns applied to the thenar muscles of a group of older, able-bodied individuals and an age-matched post-stroke group. We wanted to examine the physiological response of older healthy muscle as well as CVA-paralyzed muscle when stimulated with patterns that varied in character, comparing a constant frequency pattern (20 Hz), one that gradually increased frequency over time (20-40 Hz), and one that contained doublets.

Much research has focused on the response of muscle paralyzed by spinal injury, but not CVA-paralyzed muscle, to variable patterns of electrical stimulation (Thomas et al., 2003; Godfrey, Butler, Griffin, & Thomas, 2002; Griffin, Thomas, & Godfrey, 2001). Furthermore, the vast majority of stroke-related electrical stimulation investigations have emphasized recovery of motor control in the lower extremity, more specifically, gait training (for review, see Daly, 2006). Much less information is available on the resumption of motor control and functional use of the hand following stroke (for review, see de Kroon, Ijzerman, Chae, Lankhorst, & Zilvold, 2005). No study to date has administered variable electrical stimulation patterns to a hemiplegic population to identify the specific parameters of NMES that could most effectively facilitate motor return: information that could be vital for further development of clinical treatment regimes and post-stroke rehabilitation practice.

Overall, our findings revealed that stimulation trains that increase or contain doublets preserved force better than a constant stimulation pattern. For the able-bodied, the greatest average force, peak force, and largest FTI were generated during the doublet pattern. In the post-stroke participants, the gradually increasing 20-40 Hz pattern showed higher average forces and the highest FTI. The constant frequency train produced the lowest overall forces in both conditions.

Using doublets during stimulation proved to be effective for enhancing force temporarily and this concurred with previous work indicating that this pattern can produce greater force output (Scott et al., 2007; Allman Cheng & Rice, 2004; Scott & Binder-Macleod, 2003; Griffin et al., 2002; Binder-Macleod & Scott, 2001; Binder Macleod, Lee, & Baadte, 1997), enhance muscle performance (Maladen, et al., 2007; Kebaetse et al., 2005; Lee & Binder-Macleod, 2000) or augment force when begun after single pulse patterns (Scott et al, 2003). Doublets were most beneficial in the able-bodied, where a brief, sizable increase in force was noted. In the able-bodied, the onset of doublet pulses produced an immediate increase in force followed by a gradual decline. In contrast, we observed that doublets had an extraordinary dampening effect on the force output in paralyzed muscle. For a few of our stroke participants, the onset of the doublet pattern further diminished already negligible forces and proved to reduce what little output was present at the 90s mark (Figure 2.10, doublet pattern, trace B). A known disadvantage when using doublets is that this pattern has been noted to cause excessive fatigue (Scott et al., 2003) and recent evidence has also suggested that when a doublet initiates a stimulation train, the beneficial effect in fatigued muscle may be fleeting (Bentley & Lehman, 2005).

Average forces were significantly greater in the able bodied than the CVA condition for all of the patterns presented. Our findings clarify the marked differences between healthy and paralyzed tissue, and these differences require strong consideration when exploring electrical stimulation patterns that maximize performance in human muscle.

Evidence exists that chronically paralyzed muscle undergoes extensive physiological transformation over time. Chemical, neural, and mechanical changes are present in denervated muscle tissue that may impact transmission of peripheral electrical current and affect outcomes. Individual motor unit firing rates during the onset of a voluntary contraction as well as during maximal effort are typically reduced in the paralyzed individual and the incidence of doublets is more prevalent (Thomas et al. 2002). Contractile properties can be altered in chronic paralysis due to the loss of Type I (fatigue-resistant) fibers and the resulting predominance of Type II fibers, which make for a less fatigue tolerant tissue (Malisoux et al., 2007; Shields, 1995; Grimby, Brobery, Krotkiewska, & Krotkiewski, 1976). Individuals with a spastic motor recovery pattern show hyperactive stretch reflexes in antagonist muscles combined with weakness of agonists that can produce uncoordinated and often ineffective movement (Bourbonnais and vVanden vNoven, 1989). In contrast, individuals with a flaccid motor recovery can

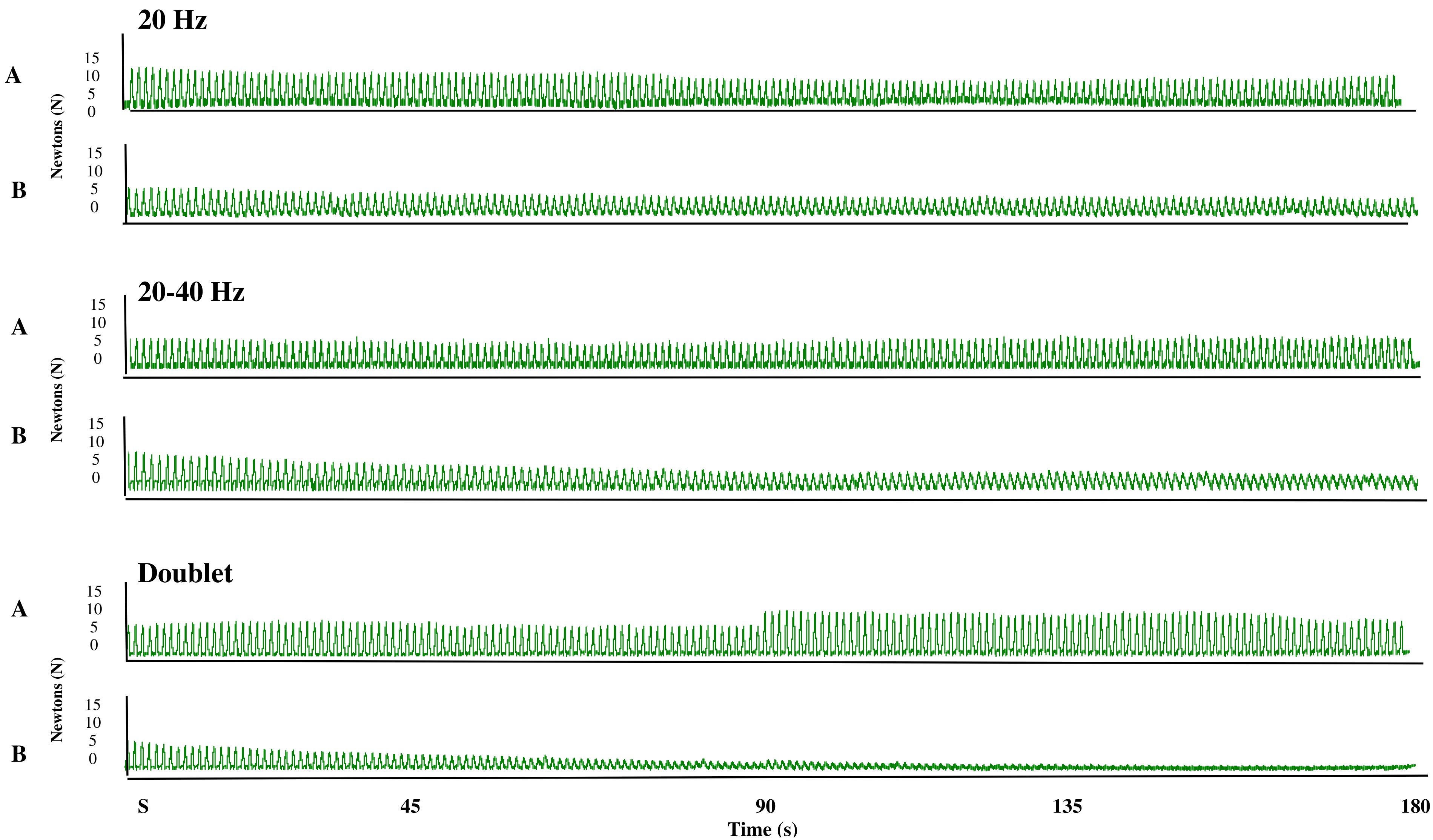



Figure 2. 10. Examples of six raw data traces for able bodied (A) and post-stroke (B) participants demonstrating force output in 20 Hz constant pattern, 20-40 Hz pattern, and doublet pattern.

experience physiological changes such as decreased muscle fiber size, density, capillarity, and bone density much like what is seen in muscles following non-use or during extended bed rest (Krasnoff& Painter, 1999). Finally, paralyzed muscle is notably weaker and has been shown to fatigue more rapidly than able-bodied muscle (Thomas et al. 2003). Paralyzed motor units of the hand have shown reduced conduction velocities and slower twitch contraction times as well (Hager-Ross, Klein, & Thomas, 2006).

Furthermore, typical neurological remodeling of motor units seen in advanced ages creates slower, less powerful muscle that fatigues more rapidly (Macaluso & DeVito, 2004; Connelly, Rice, Roos, & Vandervoort, 1999). Because stroke is most prevalent in those over age 65, paralysis in CVA is usually imposed on muscle components that have undergone age-related physiological changes such as reduced calcium concentrations within the muscle and decreased sarcolemmal excitability (Carmeli, Coleman, & Reznick, 2002). Viable motor units and muscle fibers are reduced in aged muscle, resulting in loss of strength and an increased reliance on slow twitch, fatigue-resistant Type I fibers (Allman & Rice, 2002). Greater fatigue resistance has been observed in older muscle when compared to young muscle (Rubinstein & Kamen, 2005; Lanza, Russ, & Ken-Braun, 2004) and fewer incidences of doublets in older muscle have also been reported (Christie & Kamen, 2006). The overall firing rate of motor units tends to be lower in older individuals as well (Semmler, Kornatz, & Enoka, 2003; Connelly et al., 1999). Additionally, the incidence of pathology involving neuronal changes (Drachman, 2006; Raz & Rodrigue, 2006), cardiovascular disease (Franklin, 2006), and musculoskeletal impairment (Narici & Maganaris, 2006; Blair & Carrington, 2006) increases with aging; all conditions which may present compounding factors influencing the individual response to NMES. There is also a propensity of electrical stimulation to target fast-fatigable fibers due to the lower resistance and greater conductivity of larger diameter axons (Baker et al., 2000). These factors may have contributed to the reduced overall force output seen in the post-stroke individuals.

A notable difference during our stimulation was that the muscle paralyzed by stroke was unable to sustain force during the initial 90s of constant 20 Hz that began all three patterns, losing, on average, almost half of its initial force during this period. Previous literature emphasizes the need for higher frequencies of stimulation during paralysis applications due to the inherent weakness in the muscle and rapid fatigue that results (Shields et al., 2006). Additionally, stimulation at a low frequency such as 20 Hz could exacerbate low-frequency fatigue (LFF) processes within the muscle. In an effort to combat LFF, application of higher frequencies at the onset of fatigue appears necessary. Using this strategy has been shown to enhance force and improve muscle performance in paralyzed tissue (Kebaetse et al., 2005) and supports our use of an increasing-frequency and doublet pattern applied at a point of fatigue. However, CVA-paralyzed muscle may require stimulation characteristics that maintain force *upon onset* so that any facilitation of force when fatigue ensues will be effective in maximizing overall performance; short-lived, temporary bursts of force that do not overcome total fatigue effects will probably not achieve this.

Voluntary force production in the form of MVCs of the thenar muscle group performed before and after each stimulating pattern showed the lowest decline during the 20 Hz pattern in both conditions. Although this was an intermittent presentation of pulses at a low frequency, a fatigue response, although minimal, was still present. The 20 Hz pattern generated less fatigue, but overall force production was very limited as well. Once again, this would appear to strengthen the argument that higher frequencies are required to initiate and sustain force production over time. Lower frequency pulses, especially those delivered in intermittent bursts, cannot activate and sustain the continued calcium flow needed to maximize force production from the contractile machinery.

We also investigated the impact the three patterns would have on fatigue during evoked forces. This was done to determine if LFF was apparent in the 4s stimulation trains following presentation of the fatiguing patterns. If this phenomenon were present, lower frequencies (e.g., 10 Hz and 20 Hz) would be more significantly depressed following a fatiguing stimulation pattern relative to the changes seen in the higher frequencies (30, 40 or 50 Hz) following fatigue. Our results supported this contention. In the able-bodied, the 10 Hz showed a robust difference from the remaining evoked forces in that notable force was lost when these trains were presented before and after the fatiguing patterns. In the post-stroke participants, this effect was seen at 10 Hz and 20 Hz as well. Because LFF was present in both conditions, it appears to impact healthy as well as pathologically impaired neural tissue similarly.

In summary, application of three varying patterns of neuromuscular electrical stimulation administered to the adductor pollicis of able-bodied and post-stroke individuals emphasized the neurological and behavioral differences often seen in paralyzed tissue when compared to healthy tissue. A varied stimulation pattern of doublets was most effective in maximizing force, but the repetitive presentation may have overloaded the deficient neurological apparatus of the post-stroke muscle when applied, and may have created greater fatigue. Furthermore, it appears that hemiplegic musculature has a very limited capacity to generate and maintain force when low-frequency, submaximal, or constant-pattern NMES is applied. This was evident in the downward slide of force at onset. For these participants, our increasing 20-40 Hz pattern enhanced force more so than the constant pattern without the fatiguing effect of the doublet pattern.

The outcomes of this investigation can have significant implications for applied science. The use of neuromuscular electrical stimulation for rehabilitation of pathological populations and paralyzed individuals has shown to be effective, but until specific patterns and parameters that maximize force output and delay the onset of fatigue can be clearly defined, further study is warranted. The results of our investigation further indicate that the use of electrical stimulation programs that vary in frequency, incorporate doublets, and more closely simulate physiological motor unit firing patterns may be more effective in maintaining force output and delaying the onset of fatigue than constant frequency patterns that are often used in clinical applications. Translation of this and other research into clinical practice regimes remains vital to providing effective intervention to the CVA-paralyzed individual that will improve motor function and enhance overall quality of life.

**REFERENCES**


Adam, A., & de Luca, C. J. (2005). Firing rates of motor units in human vastus lateralis muscle during fatiguing isometric contractions. *Journal of Applied Physiology, 99* (1), 268-280.

Allman, B. L., & Rice, C. L. (2004) An age-related shift in the force-frequency relationship affects quadriceps fatigability in old adults. Journal of Applied Physiology, 96 (3):1026-1032.

Aoyagi, Y., & Tsubahara, A. (2004). Therapeutic orthosis and electrical stimulation for upper extremity hemiplegia after stroke: a review of effectiveness based on evidence. *Topics in Stroke Rehabilitation, 11* (3), 9-15.

Baker, L. L., Wederich, C. L., McNeal, D. R., Newsam, C., & Waters, R. L. (2000). *Neuromuscular electrical stimulation,* (4th Ed.). Los Amigos Research & Education Institute: Downey, CA.

Bellemare, F., & Garzaniti, N. (1988). Failure of neuromuscular propagation during human maximal voluntary contraction. *Journal of Applied Physiology, 64* (3), 1084-1093.

Bentley, L. F., & Lehman, S. L. (2005). Doublets and low-frequency fatigue in potentiated human muscle. *Acta Physiologica Scandinavia, 185* (1), 51-60.

Berner,Y. N., Lif Kimchi, O., Spokoiny, V., & Finkeltov, B. (2004). The effect of electric stimulation treatment on the functional rehabilitation of acute geriatric patients with stroke-a preliminary study. *Archives of Gerontology and Geriatrics, 39* (2), 125-132.

Bickel, C. S., Slade, J. M., Warren, G. L., & Dudley, G. A. (2003). Fatigability and variable-frequency train stimulation of human skeletal muscles. *Physical Therapy. 83* (4), 366-373.

Bigland-Ritchie, B. Kulkulka C., Lippold, O. C., & Woods, J. J. (1982) The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. *Journal of Physiology, 330*, 265-278.

Bigland-Ritchie, B., Zijdewind, I., & Thomas, C. K. (2000). Muscle fatigue induced by stimulation with and without doublets. *Muscle and Nerve, 23* (9), 1348-1355.

Binder-Macleod, S. A., & McDermond (1992). Changes in the force-frequency relationship of the human quadriceps femoris muscle following electrically and voluntarily induced fatigue. *Physical Therapy, 72* (2), 95-104.

Binder-Macleod, S. A., & Scott, W. B. (2001). Comparison of fatigue produced by various electrical stimulation trains. *Acta Physiologica Scandinavia, 172,* 195-203.

Blair, H. C., & Carrington, J. L. (2006). Bone cell precursors and the pathophysiology of bone loss. *Annals of New York Academy of Science, 1068,* 244-249.

Bourbonnais, D. & Vanden Noven, S. (1989). Weakness in patients with hemiparesis. *American Journal of Occupational Therapy, 43* (5), 313-319.

Burke, R. E., Levine, D. N., Tsairis, & Zajac, F. E. (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *Journal of Physiology, 234* (3), 723-48.

Carmeli, E., Coleman, R. & Reznick, A. Z.. (2002). The biochemistry of aging muscle. *Experimental Gerontology 37* (4), 477-489.

Cauraugh, J., Light, K., Kim, S., Thigpen, M., & Behrman, A. (2000). Chronic motor dysfunction after stroke: recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. *Stroke, 31* (6), 1360-1364.

Chae, J., Bethoux, F., Bohine, T., Dobos, L., Davis, T. & Friedl, A. (1998). Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. Stroke, 29 (5), 975-979.

Chae, J., Yu, D., & Walker, M. (2001). Percutaneous intramuscular neuromuscular electrical stimulation for the treatment of shoulder subluxation and pain in chronic hemiplegia: a case report. American Journal of Physical Medicine and Rehabilitation, 80 (4), 296-301.

Chantraine, A., Baribeault, A., Uebelhart, D., & Gremion, G. (1999). Shoulder pain and dysfunction in hemiplegia: effects of functional electrical stimulation. Archives of Physical Medicine and Rehabilitation, 80 (3), 328-331.

Chen, S. C., Chen, Y. L., Chen, C. J., Lai, C. H., Chiang, W. H., & Chen, W. L. (2005). Effects of surface electrical stimulation on the muscle-tendon junction of spastic gastrocnemius in stroke patients. Disability and Rehabilitation, 27 (3), 105-110.

Christy, A., & Kamen, G. (2006). Doublet discharges in motoneurons of young and older adults. Journal of Neurophysiology, 95 (5), 2787-2795.

Connelly, D. M., Rice, C. L., Roos, M. R., & Vandervoort, A. A. (1999). Motor unit firing rates and contractile properties in tibialis anterior of young and old men. Journal of Applied Physiology, 87 (2), 843-852.

Daly, J. J. (2006). Response of gait deficits to neuromuscular electrical stimulation for stroke survivors. Expert Reviews in Neurotherapeutics, 6 (10), 1511-1522.

de Kroon, J. R., Ijzerman, M. J., Chae, J., Lankhorst, G. J., and Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *Journal of Rehabilitation Medicine, 37,* 65-74.

Dorfman, L. J., Howard, J. E., & McGill, K. C. (1990). Triphasic behavioral response of motor units to submaximal fatiguing exercise. *Muscle and Nerve, 13* (7), 621-628.

Drachman, D. A. (2006). Aging of the brain, entropy, and Alzheimer's disease. *Neurology, 67* (8), 1340-1352.

Duchateau, J. & Hainaut, K. (1986). Nonlinear summation of contractions in striated muscle. I. Twitch potentiation in human muscle**.** *Journal of Muscle Research & Cell Motility, 7*(1), 11-17.

Edwards, R. H., Hill, D. K., Jones, D. A., & Merton, P. A. (1977). Fatigue of long duration in human skeletal muscle after exercise. *Journal of Physiology (London), 272,* 769-778.

Enoka, R. M., & Fuglevand, A. J. (2001). Motor unit physiology: some unresolved issues. *Muscle and Nerve, 24* (1), 4-17.

Erim, Z., Beg, M. F., Burke, D. T., & de Luca, C. J. (1999). Effects of aging on motor-unit control properties. *Journal of Neurophysiology, 82* (5), 2081-2091.

Eskes, G. A., Butler, B., McDonald, A., Harrison, E. R., & Phillips, S. J. (2003). Limb activation effects in hemispatial neglect. *Archives of Physical Medicine and Rehabilitation 84* (3), 323-328.

Franklin, S. S. (2006). Hypertension in older people, Part 1. *Journal of Clinical Hypertension, 8* (6), 444-449.

Fuglevand, A. J., Zackowski, J. M., Huey, K. A. & Enoka, R. M. (1993) Impairment of neuromuscular propagation during human fatiguing contractions at submaximal forces. *Journal of Physiology, 460,* 549-572.

Garland, S. J., Griffin, L., Ivanova, T. (1997). Motor unit discharge rate is not associated with muscle relaxation time in sustained submaximal contractions in humans. Neuroscience Letters, 239, 25-28.

Griffin, L., Thomas, C. K., & Godfrey, C. (2001). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscle. *Journal of Neurophysiology, 87,* 2271-2278.

Griffin, L., Godfrey, S. & Thomas, C. K. (2002). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. *Journal of Neurophysiology, 87,* 2271-2278.

Griffin, L., Jun, B. G., Covington, C. & Doucet, B. M. (2006). Force output during fatigue with progressively increasing stimulation frequency. *Journal of Electromyography and Kinesiology,* [article in press]

Griffin, L., Godfrey, S. & Thomas, C. K. (2002). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. Journal of Neurophysiology, 87, 2271-2278.

Grimby, G., Brobery, C., Krotkiewska, I., & Krotkiewski, M. (1976). Muscle fiber composition in patients with traumatic cord lesions. *Scandinavian Journal of Rehabilitation Medicine, 8,* 37-42.

Gritsenko, V., & Prochazka, A. (2004). A functional electric stimulation-assisted exercise therapy system for hemiplegic hand function. *Archives of Physical Medicine and Rehabilitation 85* (6), 881-885.

Godfrey, S., Butler, J. E. Griffin, L. and Thomas, C. K. (2002) Differential fatigue of paralyzed thenar muscles by stimuli of different intensities. *Muscle Nerve 26*(1): 122-131.

Hager-Ross, Klein, & Thomas, C. K. (2006). Twitch and tetanic properties of human thenar motor units paralyzed by chronic spinal cord injury. *Journal of Neurophysiology, 96* (1), 165-174.

Hendricks, H. T., Ijzerman, M. J., de Kroon J. R., Groen F. A., & Zilvold, G. (2001). Functional electrical stimulation by means of the "Ness Handmaster Orthosis" in chronic stroke patients: an exploratory study. *Clinical Rehabilitation, 15* (2), 217-220.

Hobby, J., Taylor, P. N., & Esnouf, J. (2001). Restoration of tetraplegic hand function by use of the neurocontrol freehand system. *Journal of Hand Surgery (Britain), 26* (5), 459-464.

Jones, D. A., Bigland-Ritchie, B. R., & Edwards, R. H. T. (1979). Excitation frequency and muscle fatigue: Mechanical responses during voluntary and stimulated contractions. *Experimental Neurology, 64,* 401-413.

Karu, Z. Z., Durfee, W. K., & Barzilai, A. M. (1995). Reducing muscle fatigue in FES applications by stimulating with N-let pulse trains. IEEE Transcripts of Biomedical Engineering, 42(8), 809-817.

Kebaetse, M. B., Turner, A. E., & Binder-Macleod, S. A. (2002). Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. *Journal of Applied Physiology, 92* (1), 109-116.

Kebaetse, M. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Strategies that improve paralyzed human quadriceps femoris muscle performance during repetitive, nonisometric contractions. Archives of Physical Medicine and Rehabilitation, 86 (11), 2157-2164.

Kebaetse, M. B., & Binder-Macleod, S. A. (2004). Strategies that improve human skeletal muscle performance during repetitive, non-isometric contractions. Pflugers Archives, 448(5), 525-32.

Kesar, T. & Binder-Macleod, S. A. (2006). Effect of frequency and pulse duration on human muscle fatigue during repetitive electrical stimulation. Experimental Physiology, 91, (6), 967-976.

Keeton, R. B., & Binder-Macleod, S. A. (2006). Low-frequency fatigue. *Physical Therapy, 86* (8), 1146-1150.

Kesar, T. & Binder-Macleod, S. A. (2006). Effect of frequency and pulse duration on human muscle fatigue during repetitive electrical stimulation. *Experimental Physiology, 91* (6), 967-976.

Kimberley, T. J., Lewis, S. M., Auerbach, E. J., Dorsey, L. L., Lojovich, J. M., & Carey, J. R. (2004). Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Experimental Brain Research, 154, 450-460.*

Klein, Hager-Ross, &Thomas, C. K. (2006). Fatigue properties of human thenar motor units paralysed by chronic spinal cord injury. *Journal of Physiology, 573 (Part 1),* 161-171.

Kraft, G. H., Fitts, S. S., and Hammond, M. C. (1992). Techniques to improve function of the arm and hand in chronic hemiplegia. *Archives of Physical Medicine & Rehabilitation, 73* (3), 220-227.

Krasnoff, J. & Painter, P. (1999). The physiological consequences of bed rest and inactivity. *Advances in renal replacement therapy, 6* (2), 124-132.

Lanza, I. R., Russ, D. W., & Kent-Braun, J. A. (2004). Age-related enhancement of fatigue resistance is evident in men during both isometric and dynamic tasks. *Journal of Applied Physiology, 97* (3), 967-975.

Macaluso, A., & De Vito, G. (2004). Muscle strength, power and adaptations to resistance training in older people. *European Journal of Applied Physiology, 91* (4), 450-72.

Macefield, V. G., Fuglevand, A. J., & Bigland-Ritchie, B. (1996). Contractile properties of single motor units in human toe extensors assessed by intraneural motor axon stimulation. Journal of Neurophysiology,75 (6), 2509-2519.

Maladen, Perumal, Wexler & Binder-Macleod, S. A. (2007). Effects of Activation Pattern on Nonisometric Human Skeletal Muscle Performance. *Journal of Applied Physiology, Feb 1* [Epublished ahead of print].

Malisoux, L., Jamart, C., Delplace, K.,Nielens, H., Francaux, M., & Theisen, D. (2007). Effect of long-term muscle paralysis on human single fiber mechanics. *Journal of Applied Physiology, 102* (1), 340-34

Meyers, B. M., Nguyen, J., & Cafarelli, E. (2001). Obtaining force-frequency curves with a single 3-second train of stimuli. *Muscle and Nerve, 24* (10), 1332-1338.

Narici, M. V., & Maganaris, C. N. (2006). Adaptability of elderly human muscles and tendons to increased loading. *Journal of Anatomy, 208* (4), 433-443.

Peurala, S. H., Pitkanene, K., Sivenius, J., & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clinical Rehabilitation, 16* (7), 709-716.

Popovic, D., Stojanovic, A., Pjanovic, A., Radosavlejevic, S., Popovic, M., Jovic, S., & Vulovic, D. (1999). Clinical evaluation of the bionic glove. *Archives of Physical Medicine and Rehabilitation, 80* (3), 299-304

Powell, J., Pandyan, A. D., Granat, M., Cameron, M., & Stott, D. J. (1999). Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke, 30* (7), 1384-1389.

Preston, D. C., Venkatesh, S., Shefner, J. M., Logigian, E. L. (1994). Submaximal stimuli activate different nerve fibers populations at different sites. *Muscle and Nerve, 17* (4), 381-385.

Ratkevicius, A., & Quistorff, B. (2002). Metabolic costs of force generation for constant-frequency and catchlike-inducing electrical stimulation in human tibialis anterior muscle. *Muscle & Nerve, 25*(3), 419-426.

Raz, N. & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews, 30* (6), 730-748.

Renzenbrink, G. J., & Ijzerman, M. J. (2004). Percutaneous neuromuscular electrical stimulation (P-NMES) for treating shoulder pain in chronic hemiplegia. Effects on shoulder pain and quality of life. *Clinical Rehabilitation, 18* (4), 359-365.

Ring, H. & Rosenthal, N. (2005). Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *Journal of Rehabilitation Medicine, 37* (1), 32-36.

Robbins, S. M., Houghton, P. E., Woodbury, M. G., & Brown, J. L. (2006). The therapeutic effect of functional and transcutaneous electric stimulation on improving gait speed in stroke patients: a meta-analysis. *Archives of Physical Medicine and Rehabilitation 87* (6), 853-859.

Rubenstein, S., & Kamen, G. (2005). Decreases in motor unit firing rate during sustained maximal-effort contractions in young and older adults. *Journal of Electromyography and Kinesiology, 15* (6), 536-543.

Russ, D. W., Vandenborne, K., & Binder-Macleod, S. A. (2002). Factors in fatigue during intermittent electrical stimulation of human skeletal muscle. *Journal of Applied Physiology, 93* (2), 469-478.

Semmler, J. G., Kornatz, K. W., & Enoka, R. M. (2003). Motor-unit coherence during isometric contractions is greater in a hand muscle of older adults. *Journal of Neurophysiology,* 90 (2), 346-349.

Scott, W. B. & Binder-Macleod, S. A. (2003). Changing stimulation patterns improves performance during electrically elicited contractions. *Muscle and Nerve, 28,* 174-180.

Scott, W. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Switching stimulation patterns improves performance of paralyzed human quadriceps muscle. *Muscle and Nerve, 31* (5), 581-588.

Scott, W. B., Lee, S. C., Johnston, T. E., Binkley, J., & Binder-Macleod, S. A. (2007). Switching stimulation patterns improves performance of paralyzed human quadriceps muscle. *Muscle and Nerve, 32* (1).

Scott Bickel, C., Slade, J. M., Van Hiel, L. R., Warren, G. L., & Dudley, G. A. (2004). Variable-frequency-train stimulation of skeletal muscle after spinal cord injury. *Journal of Rehabilitation Research and Development, 41* (1), 33-40.

Shields, R. K. (1995). Fatigability, relaxation properties, and electromyographic responses of the human paralyzed soleus muscle. *Journal of Neurophysiology, (73)* 6, 2195-2206.

Shields, R. K., Dudley-Javorski, S., & Cole, K. R. (2006). Feedback-controlled stimulation enhances human paralyzed muscle performance. Journal of Applied Physiology, 101 (5), 1312-1319.

Slade, J. M., Bickel, C. S., Warren, G. L., & Dudley, G. A. (2003). Variable frequency trains enhance torque independent of stimulation amplitude.Acta Physiologica Scandinavia, 177, 87-92.

Sullivan, J. E., & Hedman, L. D. (2004). A home program of sensory and neuromuscular electrical stimulation with upper-limb task practice in a patient 5 years after a stroke. *Physical Therapy, 84* (11), 1045-1054.

Taylor, J. L., Todd, G., & Gandevia, S.C. (2006). Evidence for a supraspinal contribution to human muscle fatigue. *Clinical and Experimental Pharmacology and Physiology, 33* (4), 400-405.

Thomas, C. K., Woods, J. J., & Bigland-Ritchie, B. (1989). Impulse propagation and muscle activation in long maximal voluntary contractions. *Journal of Applied Physiology, 67* (5), 1835-1842.

Thomas, C. K., Butler, J. E., Zijdewind I. (2002). Patterns of pathological firing in human motor units. *Advances in experimental medicine and biology, 508,* 237-244.

Thomas, C. K., Griffin, L., Godfrey, S., Ribot-Ciscar, E., & Butler, J. E. (2003). Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *Journal of Neurophysiology, 89*, 202-204.

Tong, R. K., Ng, M. F., Li, L. S., & So, E. F. (2006). Gait training of patients after stroke using an electromechanical gait trainer combined with simultaneous functional electrical stimulation. *Physical Therapy, 86* (9), 1282-1294.

Van Lunteren, F., & Sankey, C. B. (2000). Catchlike property of rat diaphragm: subsequent train frequency effects in variable-train stimulation**.** *Journal of Applied Physiology, 88*(2), 586-598.

Van Lunteren, F., & Sankey, C. B. (2000). Catchlike property of rat diaphragm: subsequent train frequency effects in variable-train stimulation**.** *Journal of Applied Physiology, 88*(2), 586-598.

Wang, R. Y., Yang, Y. R. Tsai, M. W., Wang, W. T., & Chan, R. C. (2002). Effects of functional electric stimulation on upper limb motor function and shoulder range of motion in hemiplegic patients. *American Journal of Physical Medicine and Rehabilitation, 81* (4), 282-290.

Westerblad, H. & Allen, D. G. (2002). Recent advances in the understanding of skeletal muscle fatigue. *Current Opinions in Rheumatology, 14* (6), 648-652.

Yan, T., Hui-Chan, C. W., & Li, L. S. (2005). Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial. *Stroke, 36* (1), 80-85.

Zijdewind, C., Bosch, W., Goessens, L., Kandou, T. W., & Kernell, D. (1990). Electromyogram and force during stimulated fatigue tests of muscles in dominant and non-dominant hands. *European Journal of Physiology and Occupational Physiology, 60* (2), 127-132.

Zory, R., Boerio, D., Jubeau, M., & Maffiuletti, N. A. (2005). Central and peripheral fatigue of the knee extensor muscles induced by electromyostimulation. *International Journal of Sports Medicine, 26,* 847-853.

# Chapter 3: The Impact of Electrical Stimulation Frequency for Rehabilitation of the Hand in Chronic Post-Stroke Individuals

## ABSTRACT

Neuromuscular electrical stimulation (NMES) has been shown to be an effective modality in enhancing motor function following stroke, however the specific parameters that optimize motor outcomes remain unclear. Frequency of stimulation is a major determinant of successful muscle contraction which, in turn, directly impacts rehabilitation efforts. This investigation examined whether higher or lower frequencies are more effective in maximizing clinical outcomes and restoring fine motor control of the hand in a chronic post-stroke population. Sixteen chronic post-stroke individuals aged 65 ±12.50 years, an average of 4.69 ± 4.0 years post stroke participated in a one-month, 4X/week regimen of NMES applied to the thenar muscles of the hemiplegic hand. Participants received either high (40Hz) or low (20Hz) frequency stimulation. Functional skill abilities including strength, dexterity, force accuracy, and endurance were measured before and after participation in the program. Following the 4-week rehabilitation regimen, participants receiving the high frequency program showed greater gains compared to the participants receiving the low frequency intervention in thenar strength (high, 2.54 ± 0.02 vs. low, 1.28 ± 0.11 Nm), dexterity (high, 1.70 ± 1.66 vs. low, 0.87 ± 0.95 s reduction in time to complete the Minnesota Dexterity Test) and reduced error during higher force contractions (high, 36.8 ± 2.1 % vs. low, 14.5 ± 4.0% RMSE). Persons receiving the low frequency program showed greater changes in motor endurance when holding a 30% MVC contraction to endurance limit (high, 5.45 ± 1.20% decrease vs. low, 21.34 ± 3.95% increase). The results suggest that the level of NMES frequency delivered to the hand of chronic post-stroke survivors may impact specific

skills gained and that precise frequency levels could be used prescriptively for desired clinical outcomes.

## INTRODUCTION

Hemiplegia can be the most debilitating condition following stroke, and the loss of motor function of the upper extremity is a significant burden that can impair or prevent independent living. Rehabilitative therapy has the potential to facilitate return of motor function for many stroke patients. A comprehensive rehabilitation program is usually implemented shortly after stroke onset where therapists from multiple disciplines use various techniques to promote motor return in the affected limbs and body areas.

Neuromuscular electrical stimulation (NMES), sometimes referred to as functional electrical stimulation (FES) when paired with functional activity, is a modality that can be used by therapists to enhance motor recovery in the upper or lower extremities following stroke. Several studies have reported encouraging outcomes when NMES is used for gait assistance (Robbins, Houghton, Woodbury, & Brown 2006; Yan & Hui-Chan, 2005; Tong, Ng, Li, & So, 2006). NMES has also been effective in a variety of other applications used in post stroke recovery including reduction of spasticity (Yan & Hui-Chan, 2005; Ring & Rosenthal, 2005), minimization of post stroke shoulder pain (Yu et al., 2004; Chae, Yu, & Walker, 2001) and re-education of muscle for motor tasks (Cauraugh, Light, Kim, Thigpen, & Behrman, 2000; Powell, Pandyan, Granat, Cameron & Scott, 1999). Benefits in sensory awareness following NMES have been reported as well (Eskes, Butler, McDonald, Harrison, & Phillips, 2003; Sullivan & Hedman 2004; Peurala, Pitkanene, Sivenius, & Tarkka, 2002).

Less has been reported regarding the impact of NMES on fine motor control of the hand following stroke. Gritsenko & Prochazka (2004) showed improvement of hand opening skills after NMES training. Improved grasping and manipulation skills have been recorded in post-stroke individuals with hand dysfunction following both short durations (10 days) of NMES training (Santos, Zahner, McKiernan, Mahnken, & Quaney, 2006) and longer durations (3 months) of NMES training (Kraft, Fitts & Hammond, 1992). The use of NMES has also been demonstrated to improve voluntary hand control better than voluntary exercise alone (Cauraugh, et al., 2000). In a recent study, two groups of post-stroke individuals received either neurodevelopmental treatment (NDT, Bobath Method) only or NDT paired with NMES hand retraining. Only the paired group showed improvement in specific hand function (Yozbatiran, Donmez, Kayak, & Bozan, 2006). In a meta-analysis of NMES and its effectiveness for post-stroke hemiplegia, several patient groups demonstrated positive results following implementation of NMES programs when used for improvement in hand or wrist function (de Kroon, Ijzerman, Chae, Lankhorst & Zilvold, 2005). Unfortunately, few therapists readily use FES as an intervention option due to the advanced training that is often required, or restrictions in reimbursement (Cornish-Painter, Peterson, & Lindstrom-Hazel, 1996; Taylor & Humphry, 1991).

The primary obstacle for the effective use of surface or implantable NMES systems is a high rate of muscular fatigue in paralyzed muscle (Shields, 1995; Thomas, Griffin, Godfrey, Ribot-Ciscar, & Butler, 2003). Therefore, in order to avoid fatigue, NMES systems typically use constant low frequency trains to produce a smooth contraction of low force levels and avoid an early decline in force output (Bhadra & Peckham, 1997). Typical frequencies used during clinical intervention for motor recovery and relearning following stroke range from 20-30 Hz (Baker, Wederich, McNeal, Newsam, & Waters, 2000).

However, in able-bodied adults, higher frequencies are required to produce the same force output after fatigue as was demonstrated before fatigue (Edwards, Hill, Jones, & Merton,1977); therefore, a 20 Hz stimulation frequency may not provide enough force to be functional. Changing from a low (20 Hz) to a high frequency (36 Hz) enhanced functional performance by increasing the number of repetitions performed in lower extremity musculature (Kebaetse & Binder-Macleod, 2004). In a similar study, when a target of 50 degrees of active knee extension was used, a frequency of 100 Hz maximized muscle excursion but frequencies less than 20 Hz consistently failed to reach that target (Kebaetse, Turner, & Binder Macleod, 2002). It is possible that the use of higher frequencies of stimulation has not been translated into NMES-assisted stroke recovery programs because this hypothesis has not been empirically examined. Several scientific investigations have supported the benefit of NMES in improving motor function in the paralyzed population. No study to date has specifically examined the optimal stimulation frequency for restoring fine motor control in the chronic post stroke hand. This information will be useful in identifying effective clinical intervention strategies and for use in developing novel neuro-assistive devices that employ NMES to facilitate greater upper extremity function for the post stroke population.

The objective of this study was to compare changes in thenar muscle strength, dexterity, force steadiness, and endurance of the affected hand of post stroke individuals following implementation of a 1-month high- (40Hz) versus 1-month low- (20Hz) frequency electrical stimulation rehabilitation program. We hypothesized that higher frequencies of stimulation would improve strength and dexterity and that lower frequencies of stimulation would improve endurance.

## METHODS

### Study Design

This study used a single blind, quasi-experimental design.. A pretest-posttest protocol was used for measures of strength, dexterity, force accuracy and endurance. Two factors were considered, level of stimulation (high versus low) and time (pretest versus posttest). Half of the participants received the high frequency stimulation program (40 Hz) and the remaining half received the low frequency stimulation program (20 Hz).

**Participants**

Sixteen stroke survivors were recruited from the Austin, TX, vicinity through a local newspaper advertisement. Table 3.1 shows the demographics and functional status of the participants.

Individuals were selected if the following criteria were met:

- Status post stroke onset of at least 6 months prior to start of study involvement
- Full discharge from any inpatient, outpatient, or home health therapies
- In general good health without significant cognitive impairment
- Upper limb paresis with at least 20° of wrist extension, 20° wrist flexion, 30° MCP extension, and active grasp/release intact in the affected extremity
- Able to comprehend objectives of study and follow study-related directions

The exclusion criteria were: presence of extensive spasticity or flaccidity in the affected upper extremity, contraindication for the application of electrical stimulation (pacemaker, skin lesions at application site, etc.), confusion or disorientation, presence of pain syndromes of the upper extremity, or implanted surgical hardware in the hand or forearms.

**Procedure**

Participants were assigned to one of two conditions: a high frequency stimulation condition or a low frequency stimulation condition. Due to the high degree of variability found in the functional presentation of post stroke individuals, participants in the two groups were matched based on scores of the Barthel Index (Mahoney & Barthel, 1965) and the Fugl-Meyer Motor Assessment Upper Extremity Subsection (Fugl-Meyer, Jaasko, Leyman, Ollson, & Steglind, 1975) functional test batteries. This provided functional heterogeneity for both groups. Table 3.1 additionally shows a description of batteries used and norms for the Barthel Index and Fugl-Meyer tests. All participants attended an initial orientation/assessment session and signed a consent form. Participants also provided documentation of medical clearance from their personal physician before participating in the study.

At the orientation/assessment session, participants completed a short hand use questionnaire to determine any medical history relevant to upper extremity activity that could confound the study (e.g., history of orthopedic injury, surgical procedures to the hand or arm, engagement in a hand-specific exercise program). The participants' level of function was then scored using the Barthel Index (Mahoney & Barthel, 1965) and the Upper Extremity Subsection of the Fugl-Meyer Motor Assessment (Fugl-Meyer et al., 1975). At the second session, the Minnesota Manual Dexterity Test (American Guidance Service, 1969), which assesses the ability to manipulate small disks onto a board within a timed session, was administered. Functional grip and pinch strength were also assessed in all participants using grip and pinch dynamometers (Jamar, Inc.) at the second session. Following the administration of the hand function test batteries the participants were positioned in the experimental apparatus to measure thenar muscle strength, endurance and force accuracy.

Participants sat in a high-back armless chair with their affected arm placed in a custom designed table-top apparatus. A pre-fabricated metal splint (North Coast Medical Progress elbow hinge splint, NC25658) stabilized the elbow in 100° of flexion and the forearm in pronation. The splint was attached to a ½” thick sheet of laminated coreboard bolted to the laboratory table. Foam straps secured the upper arm at mid-humerus; the two forearm straps were at the wrist and just proximal to the elbow. A molded plastic orthotic was placed under the hand in the center of the palm that was contoured to support the transverse arches and the thenar and hypothenar eminences. This provided a slight lift to the palm above the surface of the coreboard and allowed the EMG electrodes on the volar surface of the hand to be unobstructed and free from any contact with the surface. The thumb was extended, abducted, and positioned against a horizontal bar housing the force transducer. The custom-designed force recording device (Mechanical Engineering Shop, University of Texas at Austin) consisted of a mobile, rotating, height-adjustable horizontal arm made of two narrow aluminum surfaces: a vertical surface that measured forces of thumb adduction (x), and a horizontal surface that measured forces of thumb extension (y). The thumb was moderately stretched into abduction to position it against the transducer surface. The contact area spanned from the thumb tip to midway between the IP and MCP joint. Figure 3.1 shows a photograph of the experimental setup.

Thumb force emanating directly from the interphalangeal joint was transferred to the transducer surface. The resultant force, R, ($R = \sqrt{x^2 + y^2}$) was calculated, displayed on the computer monitor, and recorded using commercially-available software (Spike 2, Version 5.14, Cambridge Electronics Design). The electromyographic (EMG) signal was recorded through two adhesive pre-gelled Ag/AgCl• bipolar surface electrodes 5mm in diameter (Danlee Medical Products, Inc. USA). The active electrode was placed over the thenar eminence slightly medial to the metacarpal-phalangeal joint of the thumb and the reference electrode approximately 1cm medial to the active electrode (targeting the thenar muscles: the adductor pollicis, the flexor pollicis brevis, and opponens pollicis). The third (ground) electrode was placed over the pisiform bone.

| Subject | Gender | Age | Months Post CVA | Dominant UE | Affected UE | Fugl-Meyer[a] | Barthel[b] | Funtional Use[c] |
|---|---|---|---|---|---|---|---|---|
| High-Frequency Condition | | | | | | | | |
| 1 | M | 41 | 39 | R | R | 48 | 98 | I |
| 2 | M | 70 | 78 | L | R | 58 | 100 | I |
| 3 | M | 64 | 54 | R | R | 37 | 96 | A |
| 4 | M | 67 | 91 | R | R | 62 | 100 | I |
| 5 | F | 47 | 7 | R | R | 60 | 98 | I |
| 6 | F | 60 | 27 | R | R | 63 | 97 | I |
| 7 | F | 47 | 14 | R | R | 64 | 98 | I |
| 8 | M | 65 | 104 | R | R | 34 | 93 | A |
| Mean | | 57.62 | 51.75 | | | 53.25 | 97.50 | |
| sd | | 10.97 | 36.19 | | | 12.05 | 2.26 | |
| Low-Frequency Condition | | | | | | | | |
| 1 | M | 79 | 11 | R | R | 64 | 98 | I |
| 2 | M | 74 | 247 | L | L | 43 | 97 | A |
| 3 | M | 76 | 41 | R | R | 32 | 93 | A |
| 4 | M | 76 | 52 | R | L | 58 | 98 | A |
| 5 | M | 65 | 20 | R | L | 64 | 100 | I |
| 6 | M | 58 | 120 | L | R | 59 | 98 | I |
| 7 | F | 84 | 54 | L | L | 65 | 100 | I |
| 8 | M | 73 | 33 | L | L | 45 | 97 | A |
| Mean | | 73.12 | 77.25 | | | 53.75 | 97.62 | |
| sd | | 8.14 | 77.97 | | | 12.23 | 2.19 | |

Table 3.1. [a]Scores upper extremity volitional movements such as touching ear with affected hand, touching opposite knee with affected hand, grasping items, etc.: 0 = cannot be performed, 1= can be partially performed, 2 = can be performed fully and adequately; maximum score = 66 points. [b]Scores ability to perform daily functional tasks including bathing, feeding, dressing, etc.: (weighted items) 0 = unable to perform task, 1, 2, or 3 = attempts task but unsafe; 3, 5, or 8 = moderate help required; 4, 8, or 12 = minimal help required; 5, 10, or 15 = fully independent; maximum score = 100 points. [c]Rating used to describe general level of assistance needed for affected hand function: Assisted (A) = able to use affected hand for function with assistance; Independent (I) = able to use affected hand independently.

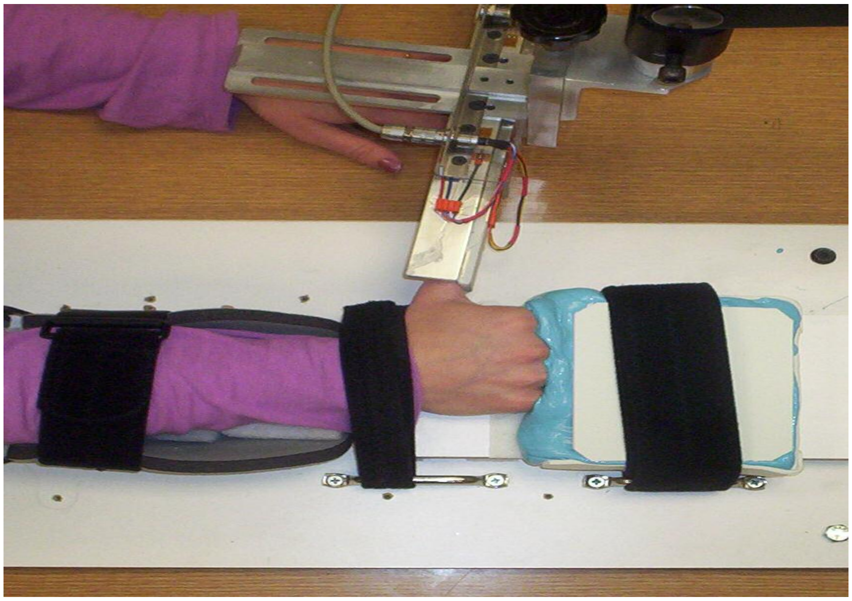


Figure 3.1. Overhead photo of upper extremity positioning of experimental set up.

All data were recorded on computer and analyzed offline using Spike 2 for Windows (version 5) software package (Cambridge Electronic Design). EMG was amplified by 100 (Coulbourn Instruments Isolated Bioamplifier with Bandpass Filter, Model V75-04), high-pass filtered above 8 Hz, sampled at 2000 Hz, and digitally converted (Micro 1401 mkII 500kHz 16-bit Analog-Digital Converter with ADC 12 Expansion, Cambridge Electronics Design). The force output signal was amplified by 100 (Bridge 8 Amplifier System, Model 74030, World Precision Instruments) sampled at 1000 Hz and low-pass filtered at 1 kHz.

Participants first performed three maximal voluntary contractions (MVCs) of thumb adduction; the average of these three trials was used as the individual's MVC. Next, they produced brief 7s thumb adduction forces targeting 5, 10, 20, 40, and 60% MVC to measure force accuracy while following a visual target line. The target line was displayed on a computer monitor placed in front of the individual while they attempted to maintain the desired percentage force level by aligning a moving cursor with the target line over the 7 second duration. Two trials of the five contractions were performed with 30 second rests between each contraction. Presentation of each percentage level was randomized across participants. EMG and force accuracy data were extracted from these tasks. Finally, to measure endurance, participants held a voluntary contraction of 30% MVC until endurance limit. Endurance limit was defined as a loss of 30% of target force level that persisted for more than 5 seconds. All experimental procedures were repeated following the 4 week training program.

**Rehabilitation Training Program**

All participants received supervised in-home training 4 times a week for 4 weeks. They returned to the laboratory after the four weeks and the same battery of tests and functional measures were administered following the rehabilitation training program.

Eight participants were assigned to the low-frequency condition. They received neuromuscular electrical stimulation (NMES) with a low-level stimulation pattern of 20Hz elicited via a portable electrical stimulation unit (300PV Empi, Inc.). The cathode was applied on the dorsum of the affected hand between the metacarpal bones of the thumb and index finger. The anode was placed at the wrist between the radius and ulna at the level of the styloid process. This configuration yielded the greatest isolated contraction of the thenar muscles into thumb adduction. The current was adjusted to an appropriate intensity level so as to elicit a tetanized contraction of 30% of the subjects' maximal voluntary contraction (MVC). Intensity was increased throughout the treatment regimen as strength changes occurred so as to maintain this level. Average percentage MVC for the month-long regimen for each subject is shown in Figure 3.2. The stimulation was delivered in a pattern that ramped up for 1 second, held at 20Hz for 10 seconds, ramped down for 1 second, and then rested for 10 seconds. This stimulation pattern was administered to the hand thenar muscle group for 40 minutes.

Eight participants were assigned to the high frequency condition. They received NMES with a high-level stimulation pattern of 40Hz elicited via the same portable electrical stimulation unit described above, using the same electrode configuration described earlier. The high frequency stimulation was also delivered at an intensity so as to elicit a tetanized contraction of approximately 30% of the participants' MVC. In this way, the effects of muscle work load were controlled.

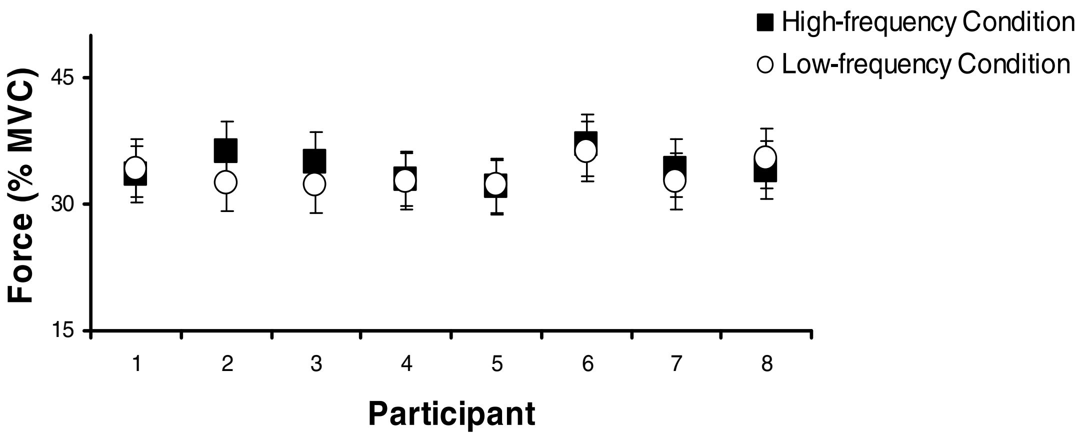



Figure 3.2. Intensity of stimulation for each participant was individualized at each session such that the thumb adductor contraction force produced was 30-35% maximal voluntary contraction (MVC) force.

The stimulation was delivered in a pattern that ramped up for 1 second, held at 40Hz for 5 seconds, ramped down for 1 second, and then rested for 5 seconds. This matched the duty cycle of the 20 Hz program such that the total number of pulses delivered per session was the same for both groups. That is, for the low-frequency protocol, 200 pulses were delivered every 20 seconds for 40 minutes (10 seconds "on", 10 seconds rest). This yielded a total of 24,000 pulses in total. For the high-frequency protocol, 200 pulses were delivered every 10 seconds for 20 minutes (5 seconds "on", 5 seconds rest) also yielding a total of 24,000 pulses delivered. The NMES program was administered to all subjects in both conditions in their homes 4 times per week for 4 weeks.

**Statistical Analysis**

To establish homogeneity of functional level between the two conditions, a Mann-Whitney Rank Sum Test was used for to compare Fugl-Meyer scores and a t-test was used to compare Barthel scores. The following variables from pre- and posttesting were calculated and compared using a 2-way repeated measures analysis of variance (ANOVA): The independent variables were time (pre versus post rehabilitation training) and condition (high-frequency versus low-frequency). Dependent variables were strength (manual grip, lateral pinch, palmar pinch, tip pinch, and thumb adductor strength), dexterity (Minnesota Dexterity test scores), force accuracy (RMS error of 7s MVC contractions), and endurance (time of 30% MVC thumb adduction force held until endurance limit). Post hoc Tukey tests discriminated pairwise multiple comparisons of significant differences. An alpha level of 0.05 was used for all statistical comparisons and significance accepted when P • 0.05. All data are presented as mean ± standard deviation throughout the text and mean ± standard error in the tables and figures.

**RESULTS**

The average Fugl-Meyer score of the high-frequency condition participants was 53.25 ± 12.05. Average score in the low-frequency condition was 53.75 ± 12.23. A maximum of 66 points can be scored on the Fugl-Meyer test. The Mann-Whitney Rank Sum Test indicated no significant differences between the scores in each condition for this battery (P = 0.79). Average Barthel Index scores (maximum score 100) in the high-frequency condition was of 97.50 ± 2.26 and those assigned to the low frequency condition scored an average of 97.62 ± 2.19. A t-test revealed no significant differences between the scores in these two condition groups as well (P = 0.91).

**Strength**

Gradual increases in strength were noted throughout the training process. Strength changes in MVC in both conditions from the second through the fourth week of training can be seen in Figure 3.3. Intensity was adjusted at each session to maintain the 30% MVC contraction level. In the high-frequency condition, average starting intensity was on day 1 of training was 19.55 ± 4.92 mA increasing to an average of 43.77 ± 15.44 mA by day 16. Overall average increase over the 4-week program: 28.27 ± 12.19 mA. Similar changes were noted in the low-frequency condition with average starting intensity on day 1 being 26.37 ± 6.71 mA and on day 16, 51.25 ± 16.81 mA. Overall average increase over the 4-week program in this condition: 27.71 ± 15.86 mA. A t-test indicated no significant differences (P=0.665) between groups in intensity changes over the course of training.

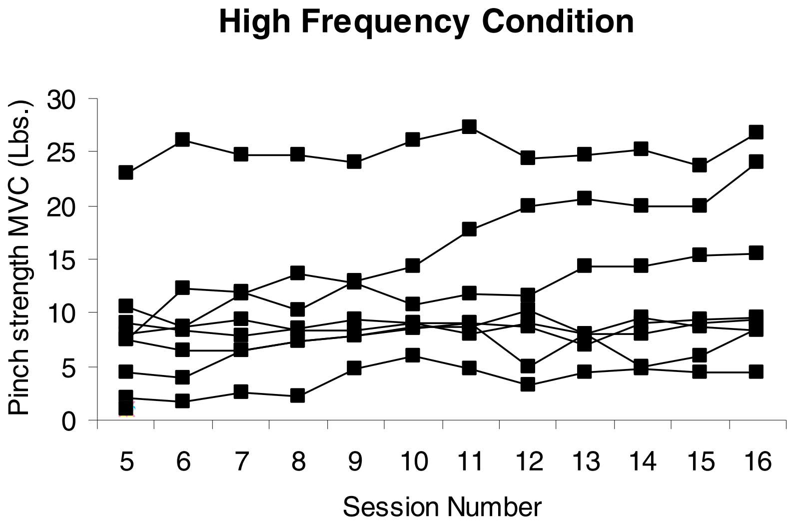
Persons in the high frequency stimulation condition showed greater average changes from pre-intervention measures to post-intervention measures than the low frequency stimulation condition in the following manual tasks: manual grip (high: 53.37 ± 6.05 pre, 58.37 ± 6.91 lbs. post; low: 60.75 ± 12.18 pre, 64.00 ± 13.18 lbs. post), lateral pinch (high: 13.87 ± 1.12 pre, 16.18 ± 1.24 lbs. post; low: 13.00 ± 2.79 pre, 13.33 ± 2.40 lbs. post), palmar pinch (high: 9.31 ± 1.80 pre, 11.25 ± 1.65 lbs. post; low: 10.06 ± 2.53 pre, 10.87 ± 2.48 lbs. post), and tip pinch (high: 6.62 ± 0.56 pre, 8.37 ± 0.80 lbs. post; low: 7.12 ± 1.66 pre, 8.00 ±1.94 lbs. post). Starting strength measures for each test were compared between conditions using t-tests and no differences were found: manual grip (P= 0.059), lateral pinch (P=0.84), palmar pinch (P=0.80), tip pinch (P=0.778) and thumb strength (P=0.560). Statistical analysis showed that there were no significant differences between condition or time for manual grip; however, the changes noted above were significant in the two of the three prehensile tasks from pre to post measures: lateral pinch (P = 0.047) and tip pinch (P = 0.003). See Figure 3.4.

The high frequency condition participants showed greater thumb adductor strength following training (high: 4.83 ± 0.25 pre, 7.38 ± 0.23 Nm post; low: 5.71 ± 0.32 pre, 6.99 ± 0.43 post). Time was a significant factor for both conditions (P=0.01). See Figure 3.5.

**Dexterity and Force Accuracy**

Participants in the high frequency condition reduced their scores (indicative of improvement) on the Minnesota Dexterity to a greater degree when compared to those in the low frequency condition. Again, t-tests showed no significant differences in starting scores (P=0.720). Average changes from pretest to posttest were significant (P = 0.03) for both conditions (high: 7.87 ± 2.00 pre, 6.16 ± 1.41 min. post; low: 6.89 ± 1.74 pre, 6.02 ± 1.40 min. post).

For the 7-second isometric contractions at the five differing MVC levels (5, 10, 20, 40 and 60% MVC) showed significant differences at the two highest contraction levels (40 and 60% MVC). The 40% MVC task was significant for time (P=0.038) and the 60% MVC task was significant for frequency condition (P=0.042). There were no significant changes in the low-frequency condition and there were also no significant differences for time in the remaining MVC tasks (5, 10, and 20% MVC). Table 3.2 shows mean RMSE before and after training for both conditions. Figure 3. shows the pretest and posttest performance of a 60% MVC in three representative subjects in the high frequency group.



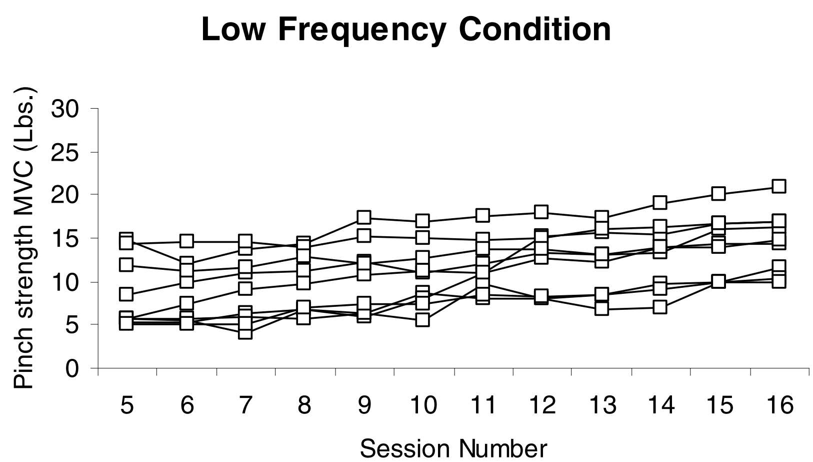




Figure 3.3. Changes observed in pinch strength MVC taken immediately before training sessions from the second through the fourth week (sessions 5 through 16).

The root mean square (RMS) of the EMG amplitude for the computer-based MVC thumb adduction showed a significant interaction between frequency condition and time (P=0.005). The high frequency group showed a significant increase from pre- to posttesting. Average RMS of the EMG amplitude for the high frequency group was 20.00 ± 0.40 mV at pretesting and 22.50 ± 0.20 mV at posttesting. Comparatively, the change in the low frequency group was 20.90 ± 0.30 mV at pretesting and 17.40 ± 0.34 mV at posttesting.

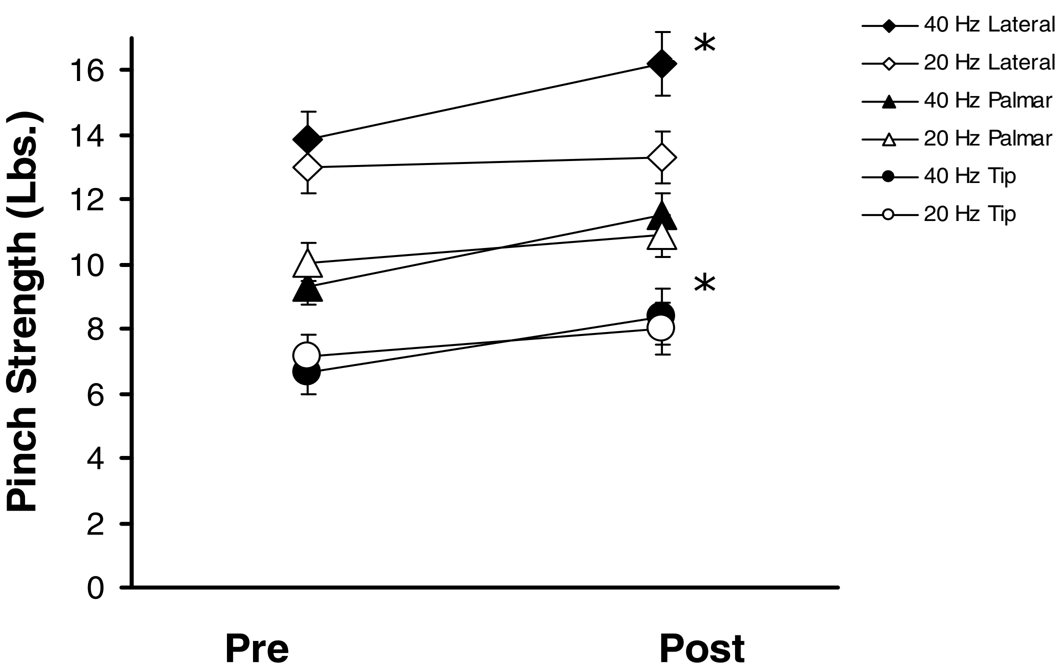



Figure 3.4. Changes seen pre and post rehabilitation training regimen in lateral pinch (diamond), palmar pinch (triangle) and tip pinch (circle). The higher frequency program showed greater increases in strength. Changes were significant from pre- to post-training in the lateral and tip pinch tasks.

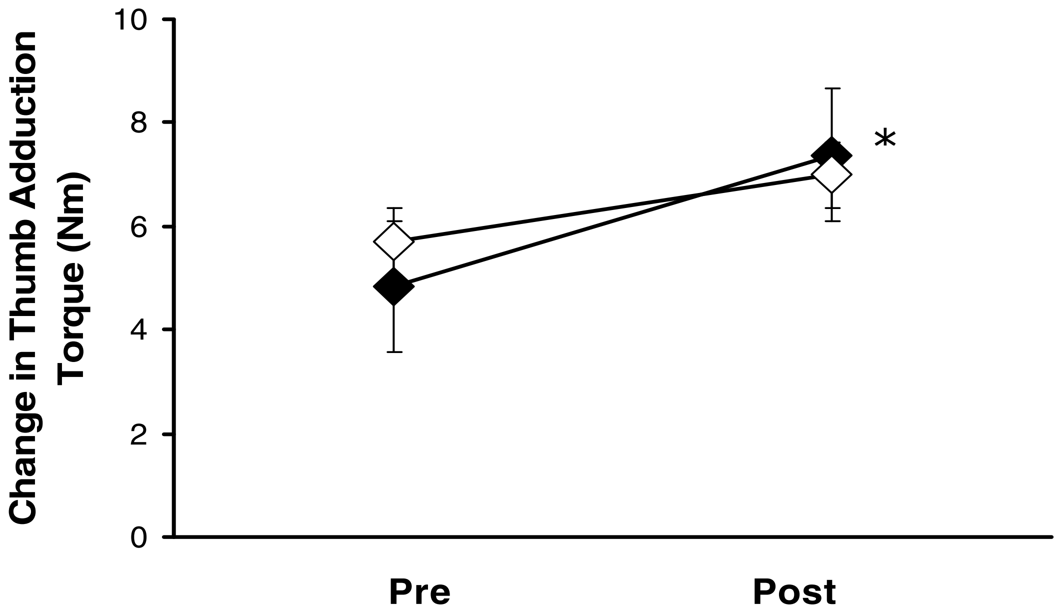



Figure 3.5. Changes in thumb adductor torque pre and post rehabilitation training. Changes were significant from pre- to posttesting in the high frequency condition

| | Pre RMSE | Post RMSE |
|---|---|---|
| 5%MVC | | |
| High | 0.012 ± 0.04 | 0.010 ± 0.004 |
| Low | 0.012 ± 0.002 | 0.009 ± 0.002 |
| 10%MVC | | |
| High | 0.022 ± 0.007 | 0.021 ± 0.005 |
| Low | 0.017 ± 0.005 | 0.018 ± 0.006 |
| 20%MVC | | |
| High | 0.022 ± 0.004 | 0.019 ± 0.003 |
| Low | 0.027 ± 0.006 | 0.022 ± 0.004 |
| 40%MVC | | |
| High | 0.031 ± 0.007 | 0.019 ± 0.003* |
| Low | 0.028 ± 0.005 | 0.025 ± 0.004 |
| 60%MVC | | |
| High | 0.060 ± 0.015 | 0.033 ± 0.004* |
| Low | 0.026 ± 0.003 | 0.032 ± 0.004 |

Table 3.2. Mean RMSE for 7s contractions at varying percentage MVC levels before and after rehabilitation training.

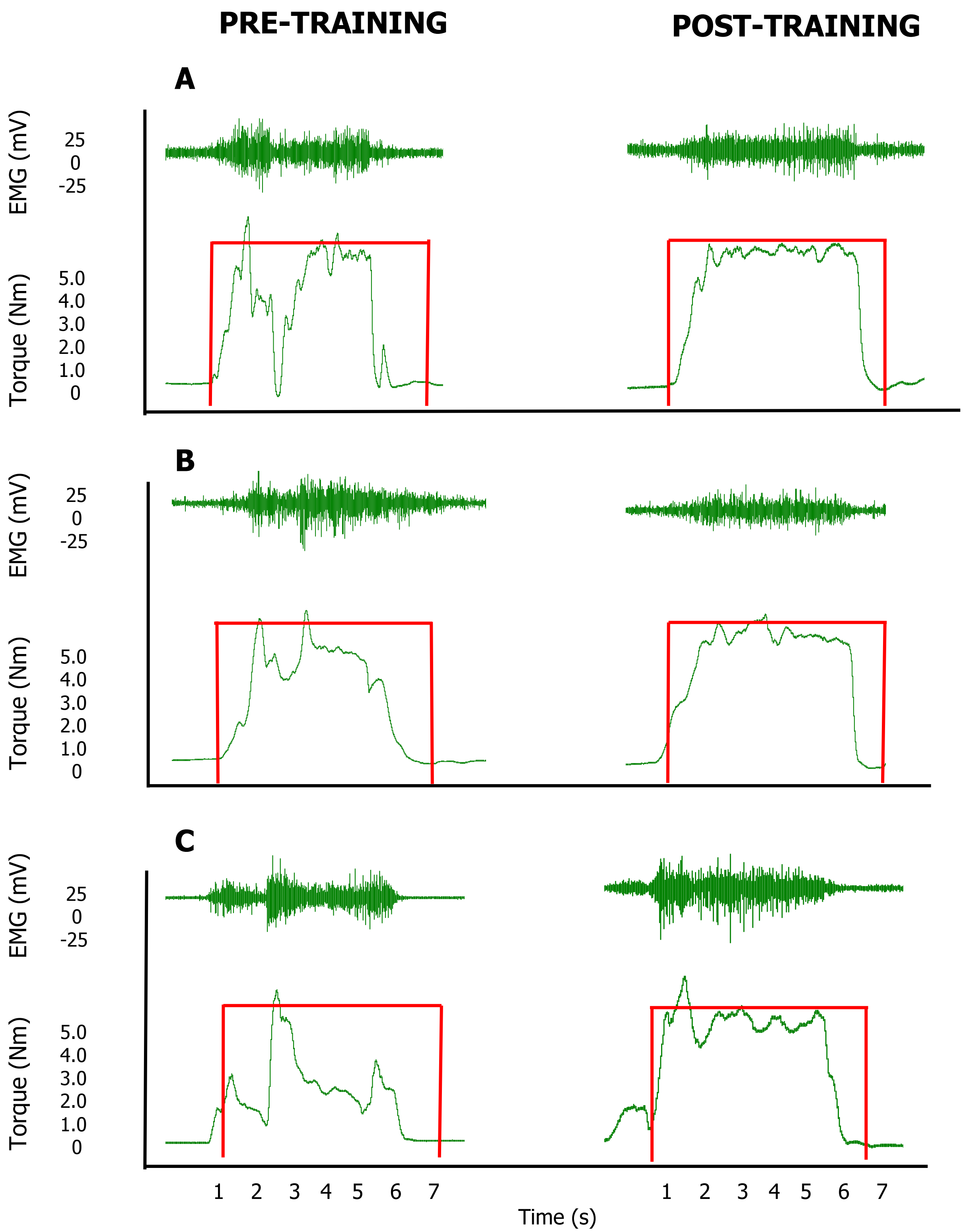

PRE-TRAINING
POST-TRAINING
A
B
C
EMG (mV)
25
0
-25
Torque (Nm)
5.0
4.0
3.0
2.0
1.0
0
1 2 3 4 5 6 7
Time (s)

Figure 3.6. Representative pre- rehabilitation training and post- rehabilitation training performance of three subjects (A, B, C) in the high-frequency condition on a 7-second 60% MVC isometric holding test. Top traces show EMG, bottom traces show torque. The red visual target line that appeared on the computer monitor to which the participant was to follow as accurately as possible is shown.

**Endurance**

Average thenar endurance in the low frequency condition were pre-intervention, 290.62 ± 59.10 s; post-intervention, 343.00 ± 69.56 s. In the high frequency condition, endurance time was 222.12 ± 39.60 s prior to rehabilitation intervention and 204.25 ± 27.09 s following intervention (Figure 3.7). There was a statistically significant interaction (P=0.02) between time and frequency for this measure, with the low frequency condition showing significantly greater changes from pre- to posttesting.

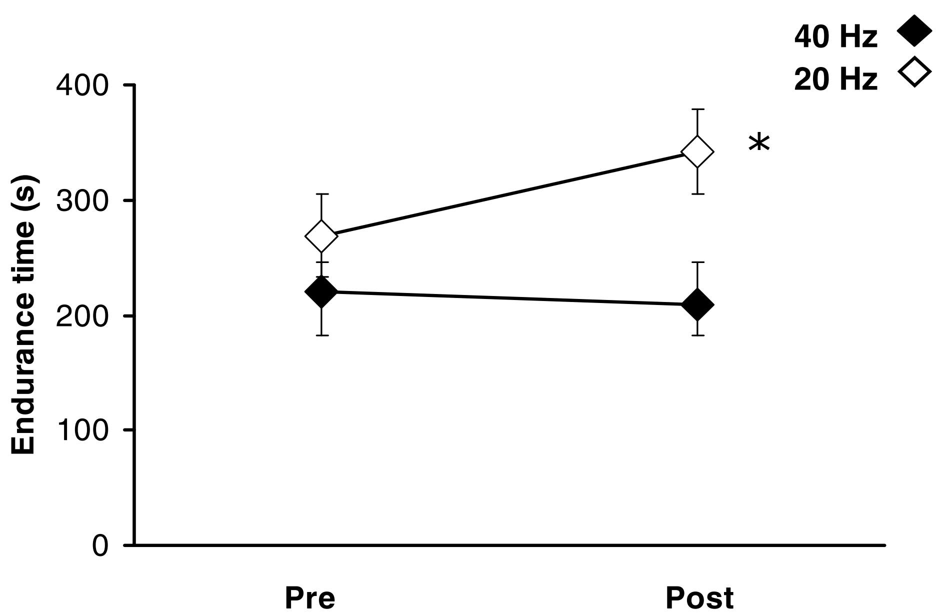



Figure 3.7. Change in endurance time seen from pre-training to post-training when participants held a 30% MVC until failure. Participants in the low-frequency condition showed significantly improved endurance time from pre- to post-testing.

## DISCUSSION

In this study, we evaluated the task-specific effects of a one-month high-frequency rehabilitation program as compared to a one-month low-frequency rehabilitation program implemented to improve the motor control of the thenar muscles in the affected hand of chronic stroke survivors. Participants in the high frequency electrical stimulation condition showed greater gains in strength, dexterity, and torque accuracy at higher level contractions when compared to participants in the low frequency stimulation condition. Individuals treated with a low frequency electrical stimulation program showed greater improvement in motor endurance.

### Strength

It is likely that neural adaptations at cortical and/or spinal levels may have facilitated the changes in motor control. The time period in our study (4-weeks) does not support development of significant muscle hypertrophy to account for the increases in maximal voluntary force capacity (for review, see Always, Siu, Murlasits, & Butler, 2005). Furthermore, both conditions underwent similar matched training regimens, maintaining 30% MVC force output throughout the 4 week period. Improvements in motor function attributable to neural adaptations to training (measured through EMG, M-wave amplitudes, and H-reflexes) have been reported following NMES programs in the gastrocnemius and soleus muscles (Jubeau, Zory, Gondin, Martin, & Maffiuletti, 2006). The biceps brachii muscle also showed an increase in torque as well as higher muscle activation evidenced by increased EMG RMS following 7 weeks of electrical stimulation training. (Colson, Martin & Van Hoecke, 2000). When healthy males were trained for 5 weeks with electrical stimulation for plantar flexion of the ankle, torque increases persisted following training and maximal M-waves and H-reflexes in the soleus remained stable even following 5 weeks of detraining (Gondin, Duclay, & Martin, 2004). Chan, Andres, Polykavskaya, & Brown (1999) studied six thenar motor units in two individuals and observed changes in contractile properties when electrical stimulation was delivered directly to the motor units three times per week for six weeks. Following training, increases in twitch, maximal tension, and fatigue resistance were observed. Our finding of increased EMG RMS values during performance of MVCs following training in the high frequency condition could also indicate neural adaptation. Increases in EMG amplitude following resistive training can signify enhanced neural drive from cortical to peripheral sites (for review, see Gabriel, Kamen, & Frost, 2006).

The bombardment of motor neurons with high frequency stimulation produces both orthodromic and antidromic propagation and has been shown to activate cortical areas more profoundly than low frequency NMES. Kampe, Jones, & Auer (2000) stimulated the median nerve in young healthy subjects at 5, 15, 40, and 100 Hz and measured simultaneous fMRI changes in the primary sensorimotor cortex. Blood oxygen levels, areas of activation, and overall tissue perfusion were seen to increase as stimulation frequency increased. NMES delivered to post-stroke individuals increased activation of primary sensory cortical areas when fMRI was used to assess changes following training (Kimberley et al, 2004). Higher, rather than lower, intensities of NMES appeared to be more effective in producing the greatest hemodynamic response in primary sensory and motor cortex areas of the lower extremity muscles following stimulation (Smith, Alon, Roys, & Gullapalli, 2003). The activation of the somatosensory cortex and sensory afferents concurrently with the motor response during NMES potentially creates a more powerful motor learning experience of movement that could have facilitated improved functional skill performance in our participants.

Participants in both conditions improved their rate of manipulation on the Minnesota Dexterity Test. This incorporates repetitive thumb-index grasps of 1-inch diameter discs followed by a short transport phase to place each disc securely in the 1-inch opening on the board situated directly below. Duque et al., (2003) suggested that persons with hemiplegia, as well as other neurological conditions that alter corticospinal processes, demonstrate ineffective scaling and coordination of fingertip forces when grasping an object. Fingertip force coordination and gradation are skills modulated by sensory and haptic (tactile) awareness, processes which have been repeatedly found to improve following training with NMES (Yozbatiran, et al., 2006; Peurala et al., 2002; Flor, Denke, Schaefer, & Grusser, 2001). Gripping velocity during the Minnesota Dexterity Test increased following an NMES training program implemented with post-stroke patients over the course of six months (Lourencao, Battistella, Martins & Litvoc, 2005). The reduction in time to perform the Minnesota Dexterity Test seen in our participants following training could have resulted from improved sensory awareness coupled with changes in grip processes. Enhanced sensation could have translated into more effective manual dexterity in the thenar muscles and thereby improved the movement plan and overall efficiency of the motor act.

**Force Accuracy**

The high frequency stimulation condition group showed more significant improvements in force accuracy during a visual tracking task at 60% MVC. Improvements in contraction steadiness against a load were seen following several weeks of resistive training with older adults and were attributed to neural adaptations (Tracy & Enoka, 2006; Tracy, Byrnes, & Enoka, 2004). Likewise, motor unit variability in the first dorsal interossei decreased when older adults participated in repetitive practice of a simple finger task; this produced fewer force fluctuations, greater steadiness during contractions, and improved overall dexterity in the hand (Kornatz, Christou, & Enoka, 2005). Because repetitive sustained contractions, such as those elicited by our high frequency NMES program, can impact motor unit discharge properties (Chan et al., 1999), the improvement in steadiness and accuracy observed in this task were likely a result of further neural adaptation facilitated through NMES. Accuracy improved significantly at only 40 and 60% MVC levels; the intervention that incorporated higher frequencies improved the functional skill areas that made use of those high motor unit firing rates.

**Endurance**

The sole functional skill that improved with lower frequency stimulation training was motor endurance. The thenar muscles of the participants in this group were trained with a program that used a lower frequency and an extended duration of stimulation; it is possible that the lower motor unit firing rates were maintained for longer time periods which resulted in greater endurance. The changes in task performance observed pre- and post-training could be a direct effect of local and sustained metabolic and cellular modifications of the muscles targeted. Enhanced glucose transport mechanisms were present in spinal-injury paralyzed quadriceps following endurance training conducted thirty minutes a day, three times per week for eight weeks (Chilibeck et al., 1999). Metabolic changes have also been observed in animal models with the implementation of endurance protocols. Nader & Esser (2001) delivered thirty minutes of 10 Hz stimulation five times per week for three weeks to rat peroneal nerves and observed increased intracellular signaling and protein synthesis similar to what is seen in endurance-type adaptations. Interestingly, our high-frequency group showed lower endurance times following training. Gondin, Guette, Jubeau, Ballay, & Martin (2006) recently suggested that following NMES training, muscles contract at higher intensities than before training. Higher intensity contractions would result in shorter endurance times.

## CONCLUSIONS

Electrical stimulation has been shown to be an effective modality to restore motor function in paralyzed muscle; however, the specific stimulation characteristics used may play an essential role in the resultant output of force and the quality of the muscular contraction elicited. Ultimately, the true end product desired in rehabilitation of paralyzed muscle using electrical stimulation is to achieve the maximal force output while minimizing fatigue. Achieving this goal will support development of muscular strength and facilitate performance of functional tasks. The specific frequencies selected for use may directly impact the skills gained. Whereas clinical frequencies typically used for rehabilitation intervention are in the 20 to 30Hz range (Baker et al., 2000) the results of the present research suggest that higher frequencies have the potential to be more effective in obtaining successful outcomes for chronic post-stroke individuals in the areas of hand strength, manual dexterity, and overall functional abilities.

## References


Alway S. E., Siu, P. M., Murlasits, Z., & Butler, D. C. Muscle hypertrophy models: applications for research on aging. *Canadian Journal of Applied Physiology, 30* (5), 591-624.

Baker, L. L., Wederich, C. L., McNeal, D. R., Newsam, C., & Waters, R. L. (2000). *Neuromuscular electrical stimulation*, (4th Ed.). Los Amigos Research & Education Institute: Downey, CA.

Bhadra, N. and Peckham, P. H. (1997). Peripheral nerve stimulation for restoration of motor function. *Journal of Clinical Neurophysiology, 14*, 5, 378-93.

Chae, J., Yu, D., & Walker, M. (2001). Percutaneous intramuscular neuromuscular electrical stimulation for the treatment of shoulder subluxation and pain in chronic hemiplegia: a case report. *American Journal of Physical Medicine and Rehabilitation, 80* (4), 296-301.

Cauraugh, J., Light, K., Kim, S., Thigpen, M. and Behrman, A. (2000). Chronic motor dysfunction in stroke. Recovering wrist and finger extension by EMG-triggered neuromuscular stimulation and bilateral movements. *Stroke, 33*, 1589-1594.

Chan, K. M., Andres, L. P., Polykavskaya, Y., & Brown, W. F. (1999). The effects of training through high-frequency electrical stimulation on the physiological properties of single human thenar motor units. *Muscle and Nerve, 22* (2), 186-195.

Chilibeck, P. D., Bell, G., Jeon, J., Weiss, C. B., Murdoch, G., MacLean, I., Ryan, E., Burnham, R. (1999). Functional electrical stimulation exercises increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle. *Metabolism, 48,* 11, 1409-1413.

Colson, S., Martin, A., & Van Hoecke, J. (2000). Re-examination of training effects by electrostimulation in the human elbow musculoskeletal system. *International Journal of Sports Medicine, 21* (4), 281-288.

Cornish-Painter, C., Peterson, C. Q., & Lindstrom-Hazel, D. K. (1996). Skill acquisition and competency testing for physical agent modality use. *American Journal of Occupational Therapy, 51* (8), 681-685.

deKroon, J. R., Ijzerman, M. J., Chae, J., Lankhorst, G. J., and Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *Journal of Rehabilitation Medicine, 37,* 65-74.

Duque, J., Thonnard, J., Vandermeeren, Y., Sebire, G., Cosnard, G., & Olivier, E. (2003). Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. *Brain, 126* (3), 732-747.

Edwards, R. H., Hill, D. K., Jones, D. A., & Merton, P. A. (1977). Fatigue of long duration in human skeletal muscle after exercise. *Journal of Physiology (London), 272,* 769-778.

Eskes, G. A., Butler, B., McDonald, A., Harrison, E. R., & Phillips, S. J. (2003). Limb activation effects in hemispatial neglect. *Archives of Physical Medicine and Rehabilitation, 84* (3), 323-328.

Flor, H., Denke, C., Schaefer, M., & Grusser, S. (2001). Effect of sensory discrimination training on cortical reorganization and phantom limb pain. *Lancet, 357* (9270), 1763-1764.

Fugl-Meyer, A. R., Jaasko, L., Leyman, I., Ollson, S., and Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine, 7*, 1, 13-31.

Gritsenko, V. and Prochazka, A. (2004). A functional electric stimulation-assisted exercise therapy system for hemiplegic hand function. *Archives of Physical Medicine and Rehabilitation, 85*, 6, 881-885.

Gondin, J., Duclay, J., & Martin, A. (2006a). Neural drive preservation following detraining after neuromuscular electrical stimulation training. *Neuroscience Letters, 409* (3), 210-214.

Gondin, J., Guette, M., Jubeau, M., Ballay, Y., Martin, A. (2006b). Central and peripheral contributions to fatigue after electrostimulation training. *Medicine and Science in Sport and Exercise, 38* (6), 1147-1156.

Jubeau, M., Zory, R., Gondin, J., Martin, A., Maffiuletti, N. A. (2006). Late neural adaptations to electrostimulation resistance training of the plantar flexor muscles. *European Journal of Applied Physiology, 98* (2), 202-211.

Kampe, K. K., Jones, D. A., & Auer, D. P. (2000). Frequency dependence of the functional MRI response after electrical median nerve stimulation. *Human Brain Mapping, 9,* 2, 106-114.

Kimberley, T. J., Lewis , S. M., Auerbach, E. J., Dorsey, L. L., Lojovic, J. M., Carey, J. R. (2004). Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Experimental Brain Research, 154* (4), 450-460

Kebaetse, M. B., & Binder-Macleod, S. A. (2004). Strategies that improve human skeletal muscle performance during repetitive, non-isometric contractions. *Pflugers Archives, 448* (5), 525-532.

Kebaetse, M. B., Turner, A. E., & Binder-Macleod, S.A. (2002). Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. *Journal of Applied Physiology, 92* (1), 109-116.

Kornatz, K. W., Christou, E. A., and Enoka, R. M. (2005). Practice reduces motor unit discharge variability in a hand muscle and improves manual dexterity in old adults. *Journal of Applied Physiology, 98* (6), 2072-2080.

Kraft, G. H., Fitts, S. S., and Hammond, M. C. (1992). Techniques to improve function of the arm and hand in chronic hemiplegia. *Archives of Physical Medicine & Rehabilitation, 73* (3), 220-227.

Lourencao, M. I., Battistella, L. R., Martins, L. C., & Litvoc, J. (2005). Analysis of the results of functional electrical stimulation on hemiplegic patients' upper extremities using the Minnesota manual dexterity test. *International Journal of Rehabilitation Research, 28* (1), 25-31.

Mahoney, F. I. and Barthel, D. W. (1965). Functional Evaluation: The Barthel Index. *Maryland State Med Journal, 14*, 61-65.

Nader, G. A., & Esser, K. A. (2001). Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. *Journal of Applied Physiology, 90* (5), 1936-1942.

Peurala, S. H., Pitkanene, K., Sivenius, J., & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clinical Rehabilitation, 16* (7), 709-716.

Powell, J., Pandyan, A. D., Granat, M., Cameron, M., & Stott, D. J. (1999). Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke, 30* (7), 1384-1389.

Ring, H. & Rosenthal, N. (2005). Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *Journal of Rehabilitation Medicine, 37* (1), 32-36.

Robbins, S. M., Houghton, P. E., Woodbury, M. G., & Brown, J. L. (2006). The therapeutic effect of functional and transcutaneous electric stimulation on improving gait speed in stroke patients: a meta-analysis. *Archives of Physical Medicine and Rehabilitation 87* (6), 853-859.

Santos, M., Zahner, L. H., McKiernan, B. J., Mahnken, J. D., & Quaney, B. (2006). Neuromuscular electrical stimulation improves severe hand dysfunction for individuals with chronic stroke: a pilot study. *Journal of Neurological Physical Therapy, 30* (4), 175-183.

Shields, R. K. (1995). Fatigability, relaxation properties, and electromyographic responses of the human paralyzed soleus muscle. *Journal of Neurophysiology, (73)* 6, 2195-2206.

Smith, G. V., Alon, G., Roys, S. R., and Gullapalli, R. P. (2003). Functional MRI determination of a dose-response relationship to lower extremity neuromuscular stimulation in healthy subjects. *Experimental Brain Research, 150*, 33-39.

Sullivan, J. E., & Hedman, L. D. (2004). A home program of sensory and neuromuscular electrical stimulation with upper-limb task practice in a patient 5 years after a stroke. *Physical Therapy, 84* (11), 1045-1054.

Taylor, E., & Humphry, R. (1991). Survey of physical agent modality use. *American Journal of Occupational Therapy, 45* (10), 924-931.

Thomas, C. K., Griffin, L., Godfrey, S., Ribot-Ciscar, E., & Butler, J. E. (2003). Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *Journal of Neurophysiology, 89* (4), 2055-2064.

Tong, R. K., Ng, M. F., Li, L. S., & So, E. F. (2006). Gait training of patients after stroke using an electromechanical gait trainer combined with simultaneous functional electrical stimulation. *Physical Therapy, 86* (9), 1282-1294.

Tracy, B. L., and Enoka, R. M. (2006). Steadiness training with light loads in the knee extensors of elderly adults. *Medicine & Science in Sports Exercise. 38*, 4, 735-745.

Tracy, B. L., Byrnes, W. C., and Enoka, R. M. (2004). Strength training reduces force fluctuations during anisometric contractions of the quadriceps femoris muscles in old adults. *Journal of Applied Physiology, 96*, 4, 1530-1540.

Yan, T., and Hui-Chan, C. W. (2005). Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial. *Stroke, 36* (1), 932-933.

Yu, D. T., Chae, J., Walker, M. E., Kirstens, A., Elovic, E. P., Flanaga, S. R., Harvey, R. L., Zorowitz, R. D., Frost, F. S., Grill, J. H., Feldstein, M. and Fang, Z. P. (2004). Intramuscular neuromuscular electric stimulation for poststroke shoulder pain: a multicenter randomized clinical trial. *Archives of Physical Medicine and Rehabilitation, 85* (5), 695-704.

Yozbatiran, N., Donmez, B., Kayak, N., and Bozan, O. (2006). Electrical stimulation of wrist and fingers for sensory and functional recovery in acute hemiplegia. *Clinical Rehabilitation, 20 (*1), 4-11.

# GENERAL DISCUSSION AND SUMMARY

The aim of this research was to explore the parameters of neuromuscular electrical stimulation (NMES) and the impact manipulation of these parameters would have during application of variable stimulation patterns. Variable pulse patterns of electrical stimulation have consistently produced better muscle performance (Van Lunteren & Sankey 2000; Binder-Macleod & Scott 2001) than constant pulse patterns. Likewise, higher intensities of stimulation are sometimes needed to enhance force output in fatigued or paralyzed muscle (Thomas, Bigland-Ritchie, & Johansson, 1991; Fuglevand, Macefield, & Bigland-Ritchie, 1999). Because intensity, frequency and pulse pattern contribute largely to the effectiveness of the resultant muscle contraction, careful consideration NMES parameters is essential. NMES has been proven effective in facilitating motor recovery following paralysis (Daly & Ruff, 2000; Chae & Yu, 2002); however, most studies have investigated NMES effects in the spinal injured population. Very little research exists on the effect of NMES used to facilitate motor recovery in the hemiplegic hand following stroke and exploration into the use of variable stimulation patterns with this population has not been previously performed.

In Study 1, we manipulated the NMES parameter of intensity comparing the effects of two variable frequency patterns and one constant frequency stimulation pattern when administered at supramaximal and submaximal intensities to the thenar muscles of young able-bodied individuals. Notable differences were seen in force output, and overall force time integrals (FTIs) . Variable stimulation patterns (the 20 Hz and doublet pattern) had an enhanced effect when administered at submaximal intensities; the force augmentation when doublets were applied was extremely pronounced, an effect not seen at supramaximal intensities. These outcomes concur with previous studies that suggest the force enhancement provided by variable pulse patterns is only seen when preceded by low frequencies (Mourselas & Granat) and that augmentation with doublets may be transient (Hager-Ross, Klein, & Thomas, 2006). More importantly, notable differences were seen between intensities, and therefore submaximal stimulation intensities may not reflect behavior of whole muscle.

In Study 2, we manipulated the population by testing variable pulse patterns in a post-stroke hemiplegic group and an age-matched healthy group. Again, notable differences were present between populations and the variable patterns administered. Overall, stimulation trains that increased or contained doublets preserved force better than a constant stimulation pattern. For the able-bodied, the greatest average force, peak force, and largest FTI were generated during the doublet pattern. In the post-stroke participants, the gradually increasing 20-40 Hz pattern showed higher average forces and the highest FTI. The constant frequency train produced the lowest overall forces in both conditions. Post-stroke participants showed a precipitous decline in force upon onset, suggesting that tissue paralyzed by stroke fatigues rapidly. Additionally, the application of a doublet pattern depressed force output even further in some of the post-stroke participants. This, too, concurs with robust evidence to suggest that repeated presentation of doublets can induce excessive fatigue (Scott et al., 2003).

In Study 3, we evaluated the task-specific effects of a one-month high-frequency rehabilitation program as compared to a one-month low-frequency rehabilitation program implemented to improve the motor control of the thenar muscles in the affected hand of chronic stroke survivors. Participants in the high frequency electrical stimulation condition showed greater gains in strength, dexterity, and torque accuracy at higher level contractions when compared to participants in the low frequency stimulation condition.

Individuals treated with a low frequency electrical stimulation program showed greater improvement in motor endurance. These outcomes suggest that training with NMES may be task-specific, and that specific parameters can be manipulated to achieve desired outcomes. Moreover, training with higher frequencies such as 40 Hz may overcome the excessive weakness present in paralyzed muscle, but not impart excessive fatigue.

The results of these investigations can be meaningful for clinical applications. The use of NMES for rehabilitation of paralyzed muscle can be incredibly effective, however, further study into specific parameters of NMES that are most effective in maximizing treatment outcomes is warranted. This information will support development of clinical strategies and rehabilitation methods that effectively and efficiently enable clincians to reach treatment goals and enable patients to achieve maximal function and quality of life.

# Bibliography

## A


Adam, A. & DeLuca, C. J. (2005). Firing rates of motor units in human vastus lateralis muscle during fatiguing isometric contractions. Journal of Applied Physiology, 99 (1), 268-280.

Allman, B. L., Cheng, A. J., & Rice, C. L. (2004). Quadriceps fatigue caused by catchlike-inducing trains is not altered in old age. Muscle and Nerve, 30 (6), 743-751.

Allman, B. L., & Rice, C. L. (2001). Incomplete recovery of voluntary isometric force after fatigue is not affected by old age. Muscle and Nerve.24 (9), 1156-1167

Allman, B. L., & Rice, C. L. (2002). Neuromuscular fatigue and aging: central and peripheral factors. *Muscle & Nerve, 25*, 785-796.

Allman, B. L., & Rice, C. L. (2004) An age-related shift in the force-frequency relationship affects quadriceps fatigability in old adults. Journal of Applied Physiology, 96 (3):1026-1032.

Alway S. E., Siu, P. M., Murlasits, Z., & Butler, D. C. Muscle hypertrophy models: applications for research on aging. Canadian Journal of Applied Physiology, 30 (5), 591-624.

American Heart Association. (2005). *Heart disease and stroke statistics – 2004 update*. Dallas, TX: www.americanheart.org.

Aoyagi, Y., & Tsubahara, A. (2004). Therapeutic orthosis and electrical stimulation for upper extremity hemiplegia after stroke: a review of effectiveness based on evidence. *Topics in Stroke Rehabilitation, 11* (3), 9-15.

**B**

Baker, L. L., Wederich, C. L., McNeal, D. R., Newsam, C., & Waters, R. L. (2000). *Neuromuscular electrical stimulation,* (4th Ed.). Los Amigos Research & Education Institute: Downey, CA.

Baldwin, E. R., Klakowicz, P. M., & Collins, D. F. (2006). Wide-pulse-width, high-frequency neuromuscular stimulation: implication for functional electrical stimulation. *Journal of Applied* Physiology 101 (1),228-240.

Bellemare, F., & Garzaniti, N. (1988). Failure of neuromuscular propagation during human maximal voluntary contraction. *Journal of Applied Physiology, 64* (3), 1084-1093.

Bentley, L. F., & Lehman, S. L. (2005). Doublets and low-frequency fatigue in potentiated human muscle. *Acta Physiologica Scandinavia, 185* (1), 51-60.

Bergstrom & Hultman (1990). Contraction characteristics of the human quadriceps muscle during percutaneous electrical stimulation. *Pfluger's Archives, 417* (2), 136-141.

Berner,Y. N., Lif Kimchi, O., Spokoiny, V., & Finkeltov, B. (2004). The effect of electric stimulation treatment on the functional rehabilitation of acute geriatric patients with stroke-a preliminary study. *Archives of Gerontology and Geriatrics, 39* (2), 125-132.

Bevan L., Laouris, Y., Reinking, R. M., & Stuart, D. G. (1992). The effect of the stimulation pattern on the fatigue of single motor units in adult cats. *Journal of Physiology, 449,* 85-108.

Bhadra, N. and Peckham, P. H. (1997). Peripheral nerve stimulation for restoration of motor function. Journal of Clinical Neurophysiology, 14, 5, 378-93.

Bickel, C. S., Slade, J. M., Warren, G. L., & Dudley, G. A. (2003). Fatigability and variable-frequency train stimulation of human skeletal muscles. *Physical Therapy. 83* (4), 366-373.

Bigland-Ritchie, B. R., Johansson, R., Lipipold, O. C. J., & Woods, J. J. (1983). Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. *Journal of Neurophysiology, 50,* 313-324.

Bigland-Ritchie, B., Jones, D. A., & Woods, J. J. (1979). Excitation frequency and muscle fatigue: electrical responses during human voluntary and stimulated contractions. *Experimental Neurology, 64* (2), 414-427.

Bigland-Ritchie, B., Kukulka, C. G., Lippold, O. C., & Woods, J. J.(1982). The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. *Journal of Physiology, 330,* 265-278.

Bigland-Ritchie, B. Zijdewind, I., & Thomas, C. K. (2000). Muscle fatigue induced by stimulation with and without doublets. *Muscle & Nerve, 23,* 1348-1355.

Binder-Macleod, S. A., & Barker, C. B. (1991). Use of a catchlike property of human skeletal muscle to reduce fatigue. *Muscle and Nerve. 1991, 14* (9), 850-857.

Binder-Macleod S. A., & Guerin, R. (1990). Preservation of force output through progressive reduction of stimulation frequency in human quadriceps femoris muscle. *Physical Therapy, 70* (10), 619-625.

Binder-Macleod, S. A., Halden, E. E., & Jungles, K. A. (1995). Effects of stimulation intensity on the physiological responses of human motor units. *Medical Science and Sports Exercise, 27* (4), 556-565.

Binder-Macleod, S. A., & Lee, S. C. (1996) Catchlike property of human muscle during isovelocity movements. *Journal of Applied Physiology, 80* (6), 2051-2059.

Binder-Macleod, S. A., Lee, S. C., & Baadte, S. A. (1997). Reduction of the fatigue-induced force decline in human skeletal muscle by optimized stimulation trains. *Archives of Physical Medicine and Rehabilitation, 78* (10), 1129-1137.

Binder-Macleod, S. A., Lee, S. C., Russ, D. W., & Kucharski, L. J. (1998). Effects of activation pattern on human skeletal muscle fatigue. Muscle & Nerve, 21, 1145-1152.

Binder-Macleod, S. A., & McDermond (1992). Changes in the force-frequency relationship of the human quadriceps femoris muscle following electrically and voluntarily induced fatigue. *Physical Therapy, 72* (2), 95-104.

Binder-Macleod, S. A., & Russ, D. W. (1999) Effects of activation frequency and force on low-frequency fatigue in human skeletal muscle. *Journal of Applied Physiology,86*(4),1337-1346.

Binder-Macleod, S. A., & Scott, W. B. (2001). Comparison of fatigue produced by various electrical stimulation trains. *Acta Physiologica Scandinavia, 172,* 195-203.

.

Blair, H. C., & Carrington, J. L. (2006). Bone cell precursors and the pathophysiology of bone loss. *Annals of New York Academy of Science, 1068,* 244-249.

Boerio, D., Jubeau, M., Zory, R., Maffiuletti, N. A. (2005). Central and peripheral fatigue after electrostimulation-induced resistance exercise. Medicine & Science in Sport and Exercise, 37 (6), 973-978.

Bourbonnais, D. & Vanden Noven, S. (1989). Weakness in patients with hemiparesis. *American Journal of Occupational Therapy, 43* (5), 313-319.

Brunt, D., Vander Linden, D. W., & Behrman, A. L. (1995). The relation between limb loading and control parameters of gait initiation in persons with stroke. Archives of Physical Medicine & Rehabilitation, 76 (7), 627-634.

Brust, J. C. M. (2000). Circulation of the brain. In Kandel, Schwartz, & Jessell (Eds.), *Principles of Neural Science* (pp.1302-1316).

Burke, R. E., Levine, D. N., Tsairis, P., & Zajac, F. E. (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. Journal of Physiology, 234 (3), 723-48.

Burke, R. E., Rudomin, P, & Zajac, F. E., (1970). Catch property in single mammalian motor units. Science, 168 (927), 122-124.

## C

Carmeli, E., Coleman, R. & Reznick, A. Z.. (2002). The biochemistry of aging muscle. *Experimental Gerontology 37* (4), 477-489.

Carmeli, Patish, & Coleman. (2003). The aging hand. *Gerontology and Biological Science and Medical Science*, 58, 146-52.

Cauraugh, J., Light, K., Kim, S., Thigpen, M. and Behrman, A. (2000). Chronic motor dysfunction in stroke. Recovering wrist and finger extension by EMG-triggered neuromuscular stimulation and bilateral movements. Stroke, 33, 1589-1594.

Chae, J., Bethoux, F., Bohine, T., Dobos, L., Davis, T., & Friedl, A. (1998). Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. *Stroke, 29* (5), 975-979.

Chae, J., & Yu, D. (2002). Neuromuscular electrical stimulation for motor restoration in hemiparesis. Topics in Stroke Rehabilitation, 8 (4), 24-39.

Chae, J., Yu, D., & Walker, M. (2001). Percutaneous intramuscular neuromuscular electrical stimulation for the treatment of shoulder subluxation and pain in chronic hemiplegia: a case report. American Journal of Physical Medicine and Rehabilitation, 80 (4), 296-301.

Chan, K. M., Andres, L. P., Polykavskaya, Y., & Brown, W. F. (1999). The effects of training through high-frequency electrical stimulation on the physiological properties of single human thenar motor units. Muscle and Nerve, 22 (2), 186-195.

Chantraine, A., Baribeault, A., Uebelhart, D., & Gremion, G. (1999). Shoulder pain and dysfunction in hemiplegia: effects of functional electrical stimulation. *Archives of Physical Medicine and Rehabilitation, 80* (3), 328-331.

Chen, S. C., Chen, Y. L., Chen, C. J., Lai, C. H., Chiang, W. H., & Chen, W. L. (2005). Effects of surface electrical stimulation on the muscle-tendon junction of spastic gastrocnemius in stroke patients. *Disability and Rehabilitation, 27* (3), 105-110.

Chilibeck, P. D., Bell, G., Jeon, J., Weiss, C. B., Murdoch, G., MacLean, I., Ryan, E., Burnham, R. (1999). Functional electrical stimulation exercises increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle. Metabolism, 48, 11, 1409-1413.

Chin, E. R., Balnave, C. D., & Allen, D. G. (1997). Role of intracellular calcium and metabolites in low-freqency fatigue of mouse skeletal muscle. American Journal of Physiology and Cellular Physiology, 272, C550-C559.

Christy, A., & Kamen, G. (2006). Doublet discharges in motoneurons of young and older adults. *Journal of Neurophysiology, 95* (5), 2787-2795.

Colson, S., Martin, A., & Van Hoecke, J. (2000). Re-examination of training effects by electrostimulation in the human elbow musculoskeletal system. International Journal of Sports Medicine, 21 (4), 281-288.

Connelly, D. M., Rice, C. L., Roos, M. R., & Vandervoort, A. A. (1999). Motor unit firing rates and contractile properties in tibialis anterior of young and old men. *Journal of Applied Physiology, 87* (2), 843-852.

Conwit, R. A., Stashuk, D., Suzuki, H., Lynch, N., Schrager, M., & Metter, E. J. ( 2000). Fatigue effects on motor unit activity during submaximal contractions. *Archives of Physical Medicine and Rehabilitation, 81* (9), 1211-1216.

Cooper, S. & Eccles, J. C. (1930). The isometric responses of mammalian muscles. Journal of Physiology, 69, 377-385.

Cornish-Painter, C., Peterson, C. Q., & Lindstrom-Hazel, D. K. (1996). Skill acquisition and competency testing for physical agent modality use. American Journal of Occupational Therapy, 51 (8), 681-685.

**D**

Daly, J. J. (2006). Response of gait deficits to neuromuscular electrical stimulation for stroke survivors. *Expert Reviews in Neurotherapeutics, 6* (10), 1511-1522.

deKroon, J. R., Ijzerman, M. J., Chae, J., Lankhorst, G. J., and Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. Journal of Rehabilitation Medicine, 37, 65-74.

Dorfman, L. J., Howard, J. E., & McGill, K. C. (1990). Triphasic behavioral response of motor units to submaximal fatiguing exercise. *Muscle and Nerve, 13* (7), 621-628.

Drachman, D. A. (2006). Aging of the brain, entropy, and Alzheimer's disease. *Neurology, 67* (8), 1340-1352.

Duchateau, J. & Hainaut, K. (1986). Nonlinear summation of contractions in striated muscle I. Twitch potentiation in human muscle**.** *Journal of Muscle Research & Cell Motility, 7*(1), 11-17.

Duque, J., Thonnard, J., Vandermeeren, Y., Sebire, G., Cosnard, G., & Olivier, E. (2003). Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. Brain, 126 (3), 732-747.

**E**

Eberstein, A., & Eberstein, S. (1996). Electrical stimulation of denervated muscle: is it worthwhile? *Medical Science of Sport and Exercise, 28* (12), 1463-1469.

Edwards, R. H., Hill, D. K., Jones, D. A., & Merton, P. A. (1977). Fatigue of long duration in human skeletal muscle after exercise. *Journal of Physiology (London), 272,* 769-778.

Enoka, R. M., & Fuglevand, A. J. (2001). Motor unit physiology: some unresolved issues. *Muscle and Nerve, 24* (1), 4-17.

Enoka, R. M., & Stuart, D. G. (1992). Neurobiology of muscle fatigue. *Journal of Applied Physiology, 72,* 1631-1648.

Erim, Z., Beg, M. F., Burke, D. T., & de Luca, C. J. (1999). Effects of aging on motor-unit control properties. *Journal of Neurophysiology, 82* (5), 2081-2091.

Eskes, G. A., Butler, B., McDonald, A., Harrison, E. R., & Phillips, S. J. (2003). Limb activation effects in hemispatial neglect. *Archives of Physical Medicine and Rehabilitation 84* (3), 323-328.

**F**

Farmer, S. F., Swash, M., Ingram, D. A., & Stephens, J. A. (1993). Changes in motor unit synchronization following central nervous lesions in man. *Journal of Physiology, 463*, 83-105

Fink, J. N. (2005). Underdiagnosis of right-brain stroke. *The Lancet, 366* (9483), 349-351.

Flor, H., Denke, C., Schaefer, M., & Grusser, S. (2001). Effect of sensory discrimination training on cortical reorganization and phantom limb pain. Lancet, 357 (9270), 1763-1764.

Franklin, S. S. (2006). Hypertension in older people, Part 1. *Journal of Clinical Hypertension, 8* (6), 444-449.

Fugl-Meyer, A. R., Jaasko, L., Leyman, I., Ollson, S., and Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scandinavian Journal of Rehabilitation Medicine, 7, 1, 13-31.

Fuglevand, A. J., Keen, D. A. (2003). Reevaluation of muscle wisdom in the human adductor pollicis using physiological rates of stimulation. *Journal of Physiology, 549,* 865-75.

Fuglevand, A. J., Macefield, V. G., & Bigland-Ritchie, B. (1999). Force-frequency and fatigue properties of motor units in muscles that control digits of the human hand. *Journal of Neurophysiology, 81,* 1718-1729.

Fuglevand, A. J., Zackowski, J. M., Huey, K. A. & Enoka, R. M. (1993) Impairment of neuromuscular propagation during human fatiguing contractions at submaximal forces. *Journal of Physiology, 460,* 549-572.

**G**

Gandevia, S. C. (1991). Spinal and supraspinal factors in human muscle fatigue. Physiological Reviews, 81, 1725-1789.

Garland, S. J., Griffin, L., Ivanova, T. (1997). Motor unit discharge rate is not associated with muscle relaxation time in sustained submaximal contractions in humans. Neuroscience Letters, 239, 25-28.

Gibson, A. S., Lambert, M. I., & Noakes, T. D. (2001). Neural control of force output during maximal and submaximal exercise. *Sports Medicine, 31* (9), 637-650.

Godfrey, S., Butler, J. E. Griffin, L. and Thomas, C. K. (2002) Differential fatigue of paralyzed thenar muscles by stimuli of different intensities. *Muscle Nerve 26*(1): 122-131.

Gondin, J., Duclay, J., & Martin, A. (2006a). Neural drive preservation following detraining after neuromuscular electrical stimulation training. Neuroscience Letters, 409 (3), 210-214.

Gondin, J., Guette, M., Jubeau, M., Ballay, Y., Martin, A. (2006b). Central and peripheral contributions to fatigue after electrostimulation training. Medicine and Science in Sport and Exercise, 38 (6), 1147-1156.

Gorgey, A. S., Mahoney, E., Kendall, T., & Dudley, T. J. (2006). Effects of neuromuscular electrical stimulation parameters on specific tension. *European Journal of Applied Physiology, 97* (6), 737-744.

Green, H. J. (1997). Mechanisms of muscle fatigue in intense exercise. *Journal of Sports Science, 15* (3), 247-256.

Gregory, C. M., Dixon, W., & Bickel C. S. (2007). Impact of varying pulse frequency and duration on muscle torque production and fatigue. Muscle and Nerve, Jan 17 [Epublished ahead of print].

Griffin, L., & Cafarelli, E. (2006). Transcranial stimulation during resistance training of the tibialis anterior muscle. *Journal of Electromyography & Kinesiology,* (in press).

Griffin, L., Garland, S. J. and Ivanova, T. (2000). Role of limb movement in the modulation of motor unit discharge during fatiguing contractions. *Experimental Brain Research, 130*, 392-400.

Griffin, L., Godfrey, S. & Thomas, C. K. (2002). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. *Journal of Neurophysiology, 87,* 2271-2278.

Griffin, L., Jun, B. G., Covington, C. & Doucet, B. M. (2006). Force output during fatigue with progressively increasing stimulation frequency. *Journal of Electromyography and Kinesiology,* [article in press]

Griffin, L., Godfrey, S. & Thomas, C. K. (2002). Stimulation pattern that maximizes force in paralyzed and control whole thenar muscles. Journal of Neurophysiology, 87, 2271-2278.

Gritsenko, V. and Prochazka, A. (2004). A functional electric stimulation-assisted exercise therapy system for hemiplegic hand function. Archives of Physical Medicine and Rehabilitation, 85, 6, 881-885.

Grimby, G., Brobery, C., Krotkiewska, I., & Krotkiewski, M. (1976). Muscle fiber composition in patients with traumatic cord lesions. *Scandinavian Journal of Rehabilitation Medicine, 8,* 37-42.

## H

Hager-Ross, Klein, & Thomas, C. K. (2006). Twitch and tetanic properties of human thenar motor units paralyzed by chronic spinal cord injury. *Journal of Neurophysiology, 96* (1), 165-174.

Hanchard, N. C. A., Williamson, M, Caley, R. W., and Cooper, R. G. (1998). Electrical stimulation of human tibialis anterior: (A) contractile properties are stable over a range of submaximal voltages; (B) high- and low-frequency fatigue are inducible and reliably assessable at submaximal voltages. Clinical Rehabilitation, 12, 413-427.

Hendricks, H. T., Ijzerman, M. J., de Kroon J. R., Groen F. A., & Zilvold, G. (2001). Functional electrical stimulation by means of the "Ness Handmaster Orthosis" in chronic stroke patients: an exploratory study. *Clinical Rehabilitation, 15* (2), 217-220.

Hobby, J., Taylor, P. N., & Esnouf, J. (2001). Restoration of tetraplegic hand function by use of the neurocontrol freehand system. *Journal of Hand Surgery (Britain), 26* (5), 459-464.

**J**

Jones, D. A., Bigland-Ritchie, B. R., & Edwards, R. H. T. (1979). Excitation frequency and muscle fatigue: Mechanical responses during voluntary and stimulated contractions. *Experimental Neurology, 64,* 401-413

Jubeau, M., Zory, R., Gondin, J., Martin, A., Maffiuletti, N. A. (2006). Late neural adaptations to electrostimulation resistance training of the plantar flexor muscles. European Journal of Applied Physiology, 98 (2), 202-211.

**K**

Kampe, K. K., Jones, D. A., & Auer, D. P. (2000). Frequency dependence of the functional MRI response after electrical median nerve stimulation. Human Brain Mapping, 9, 2, 106-114.

Karu, Z. Z., Durfee, W. K., & Barzilai, A. M. (1995). Reducing muscle fatigue in FES applications by stimulating with N-let pulse trains. IEEE Transcripts of Biomedical Engineering, 42(8), 809-817.

Kebaetse, M. B., & Binder-Macleod, S. A. (2004). Strategies that improve human skeletal muscle performance during repetitive, non-isometric contractions. Pflugers Archives, 448 (5), 525-532.

Kebaetse, M. B., Lee, S. C., & Binder-Macleod, S. A. (2001) A novel stimulation pattern improves performance during repetitive dynamic contractions. Muscle and Nerve, 24 (6), 744-752.

Kebaetse, M. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Strategies that improve paralyzed human quadriceps femoris muscle performance during repetitive, nonisometric contractions. Archives of Physical Medicine and Rehabilitation, 86 (11), 2157-2164.

Kebaetse, M. B., Turner, A. E., & Binder-Macleod, S.A. (2002). Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. Journal of Applied Physiology, 92 (1), 109-116.

Keeton, R. B., & Binder-Macleod, S. A. (2006). Low-frequency fatigue. *Physical Therapy, 86* (8), 1146-1150.

Keen, D. A., Yue, G. H., & Enoka, R. M. (1994). Training-related enhancement in the control of motor output in elderly humans. *Journal of Applied Physiology, 77,* 2648-2658.

Kesar, T. & Binder-Macleod, S. A. (2006). Effect of frequency and pulse duration on human muscle fatigue during repetitive electrical stimulation. Experimental Physiology, 91, (6), 967-976.

Kesar, T., Chou, L. W., & Binder-Macleod, S. A. (2007). Effects of stimulation frequency versus pulse duration modulation on muscle fatigue. *Journal of Electromyography & Kinesiology, Feb 20,* [Epublished ahead of print].

Kimberley, T. J., Lewis , S. M., Auerbach, E. J., Dorsey, L. L., Lojovic, J. M., Carey, J. R. (2004). Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. Experimental Brain Research, 154 (4), 450-460.

Klein, Hager-Ross, &Thomas, C. K. (2006). Fatigue properties of human thenar motor units paralysed by chronic spinal cord injury. *Journal of Physiology, 573 (Part 1),* 161-171.

Kluding, P., & Billinger, S. A. (2005). Exercise-induced changes of the upper extremity in chronic stroke survivors. *Topics in Stroke Rehabilitation, 12* (1), 58-68.

Kornatz, K. W., Christou, E. A., and Enoka, R. M. (2005). Practice reduces motor unit discharge variability in a hand muscle and improves manual dexterity in old adults. Journal of Applied Physiology, 98 (6), 2072-2080.

Kraft, G. H., Fitts, S. S., and Hammond, M. C. (1992). Techniques to improve function of the arm and hand in chronic hemiplegia. Archives of Physical Medicine & Rehabilitation, 73 (3), 220-227.

Krasnoff, J. & Painter, P. (1999). The physiological consequences of bed rest and inactivity. *Advances in renal replacement therapy, 6* (2), 124-132.

**L**

Laidlaw, D. H., Bilodeau, M., & Enoka, R. M. (2000). Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle & Nerve, 23,* 600-612.

Laufer, Y., Ries, J. D., Leininger, P. M., & Alon, G. (2001). Quadriceps femoris muscle torques and fatigue generated by neuromuscular electrical stimulation with three different waveforms. *Physical Therapy, 81* (7), 1307-1316.

Lanza, I. R., Russ, D. W., & Kent-Braun, J. A. (2004). Age-related enhancement of fatigue resistance is evident in men during both isometric and dynamic tasks. *Journal of Applied Physiology, 97* (3), 967-975.

Lee, S. C., Becker, C. N., & Binder-Macleod, S. A. (2000). Activation of human quadriceps femoris muscle during dynamic contractions: effects of load on fatigue. *Journal of Applied Physiology, 89* (3), 926-936.

Lee, S. C., & Binder-Macleod, S. A. (2000). Effects of activation frequency on dynamic performance of human fresh and fatigued muscles. *Journal of Applied Physiology,88* (6), 2166-2175.

Liberson, W. T., Holmquest, H. J., Scott, D., & Dow, M. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of gait of hemiplegia patients. *Archives of Physical Medicine & Rehabilitation, 42*, 101-105.

Lieber, R. L, & Kelly, M. J. (1996). Torque history of electrically stimulated quadriceps: Implications for stimulation therapy. *Journal of Orthopedic Research, 11* (1), 131-141.

Lourencao, M. I., Battistella, L. R., Martins, L. C., & Litvoc, J. (2005). Analysis of the results of functional electrical stimulation on hemiplegic patients' upper extremities using the Minnesota manual dexterity test. International Journal of Rehabilitation Research, 28 (1), 25-31.

## M

Macaluso, A., & De Vito, G. (2004). Muscle strength, power and adaptations to resistance training in older people. *European Journal of Applied Physiology, 91* (4), 450-72.

Macefield, V. G., Fuglevand, A. J., & Bigland-Ritchie, B. (1996). Contractile properties of single motor units in human toe extensors assessed by intraneural motor axon stimulation. Journal of Neurophysiology,75 (6), 2509-2519.

MacIntosh, B. R., & Willis, J. C. (2000). Force-frequency relationship and potentiation in mammalian skeletal muscle. Journal of Applied Physiology, 88(6), 2088-2096.

Mahoney, F. I. and Barthel, D. W. (1965). Functional Evaluation: The Barthel Index. Maryland State Med Journal, 14, 61-65.

Maladen, Perumal, Wexler & Binder-Macleod, S. A. (2007). Effects of Activation Pattern on Nonisometric Human Skeletal Muscle Performance. *Journal of Applied Physiology, Feb 1* [Epublished ahead of print].

Malisoux, L., Jamart, C., Delplace, K.,Nielens, H., Francaux, M., & Theisen, D. (2007). Effect of long-term muscle paralysis on human single fiber mechanics. *Journal of Applied Physiology, 102* (1), 340-34

Marsden, C. D., Meadows, J. C., Merton, P. A. (1983). Muscular wisdom" that minimizes fatigue during prolonged effort in man: peak rates of motoneuron discharge and slowing of discharge during fatigue. *Advances in Neurology, 39*, 169-211.

Meyers, B. M., Nguyen, J., & Cafarelli, E. (2001). Obtaining force-frequency curves with a single 3-second train of stimuli. *Muscle and Nerve, 24* (10), 1332-1338.

Miller, C., & Thepaut-Mathieu, C. (1993). Strength training by electrostimulation conditions for efficacy. *International Journal of Sports Medicine, 14* (1), 20-28.

Mourselas, N., & Granat, N. H. (1998). Evaluation of patterned stimulation for use in surface functional electrical stimulation systems. *Medical Engineering and Physics, 20* (5), 319-324.

Muller, G. R., Neuper, C., Rupp, R., Keinrath, C., Gerner, H. J., & Pfurtscheller, G. (2003). Event-related beta EEG changes during wrist movements induced by functional electrical stimulation of forearm muscles in man. *Neuroscience Letters, 340* (2), 143-147.

**N**

Nader, G. A., & Esser, K. A. (2001). Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. Journal of Applied Physiology, 90 (5), 1936-1942.

Narici, M. V., & Maganaris, C. N. (2006). Adaptability of elderly human muscles and tendons to increased loading. *Journal of Anatomy, 208* (4), 433-443.

**P**

Pedretti, L. W. (1996). *Occupational therapy for physical dysfunction*. New York: Mosby.

Peurala, S. H., Pitkanene, K., Sivenius, J., & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. Clinical Rehabilitation, 16 (7), 709-716.

Pitcher, J. B., Ridding, M. C., Miles, T. S. (2003). Frequency dependent, bi-directional plasticity in motor cortex of human adults. *Clinical Neurophysiology, 114,* 1265-1271.

Popovic, D., Stojanovic, A., Pjanovic, A., Radosavlejevic, S., Popovic, M., Jovic, S., & Vulovic, D. (1999). Clinical evaluation of the bionic glove. *Archives of Physical Medicine and Rehabilitation, 80* (3), 299-304

Powell, J., Pandyan, A. D., Granat, M., Cameron, M., & Stott, D. J. (1999). Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke, 30 (7), 1384-1389.

Popovic, M.B., Popovic, D.B., Sinkjaer,T., Stefanovic, A., & Schwirtlich, L. (2002). Restitution of reaching and grasping promoted by functional electrical therapy. *Artificial Organs, 26* (3), 271-275.

Preston, D. C., Venkatesh, S., Shefner, J. M., Logigian, E. L. (1994). Submaximal stimuli activate different nerve fibers populations at different sites. *Muscle and Nerve, 17* (4), 381-385.

**R**

Ratkevicius, A., & Quistorff, B. (2002). Metabolic costs of force generation for constant-frequency and catchlike-inducing electrical stimulation in human tibialis anterior muscle. *Muscle & Nerve, 25*(3), 419-426.

Raz, N. & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews, 30* (6), 730-748.

Renzenbrink, G. J., & Ijzerman, M. J. (2004). Percutaneous neuromuscular electrical stimulation (P-NMES) for treating shoulder pain in chronic hemiplegia. Effects on shoulder pain and quality of life. *Clinical Rehabilitation, 18* (4), 359-365.

Rich, M. M. (2006). The control of neuromuscular transmission in health and disease. *Neuroscientist, 12* (2), 134-142.

Ring, H. & Rosenthal, N. (2005). Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. Journal of Rehabilitation Medicine, 37 (1), 32-36.

Robbins, S. M., Houghton, P. E., Woodbury, M. G., & Brown, J. L. (2006). The therapeutic effect of functional and transcutaneous electric stimulation on improving gait speed in stroke patients: a meta-analysis. Archives of Physical Medicine and Rehabilitation 87 (6), 853-859.

Rubenstein, S., & Kamen, G. (2005). Decreases in motor unit firing rate during sustained maximal-effort contractions in young and older adults. Journal of Electromyography and Kinesiology, 15 (6), 536-543.

Russ, D. W., & Binder-Macleod, S. A. (1999) Variable-frequency trains offset low-frequency fatigue in human skeletal muscle. *Muscle and Nerve, 22* (7), 874-882.

Russ, D. W., Vandenborne, K., & Binder-Macleod, S. A. (2002). Factors in fatigue during intermittent electrical stimulation of human skeletal muscle. *Journal of Applied Physiology, 93* (2), 469-478.

**S**

Santos, M., Zahner, L. H., McKiernan, B. J., Mahnken, J. D., & Quaney, B. (2006). Neuromuscular electrical stimulation improves severe hand dysfunction for individuals with chronic stroke: a pilot study. Journal of Neurological Physical Therapy, 30 (4), 175-183.

Semmler, J. G., Kornatz, K. W., & Enoka, R. M. (2003). Motor-unit coherence during isometric contractions is greater in a hand muscle of older adults. *Journal of Neurophysiology,* 90 (2), 346-349.

Scott, W. B. & Binder-Macleod, S. A. (2003). Changing stimulation patterns improves performance during electrically elicited contractions. *Muscle and Nerve, 28,* 174-180.

Scott, W. B., Lee, S. C., Johnston, T. E., & Binder-Macleod, S. A. (2005). Switching stimulation trains improves performance of paralyzed human quadriceps muscle. *Muscle and Nerve, 31* (5), 581-588.

Scott, W. B., Lee, S. C., Johnston, T. E., Binkley, J., & Binder-Macleod, S. A. (2007). Effect of electrical stimulation pattern on the force responses of paralyzed human quadriceps muscles. *Muscle and Nerve, Jan 9* [Epublished ahead of print]

Scott Bickel, C., Slade, J. M., Van Hiel, L. R., Warren, G. L., & Dudley, G. A. (2004). Variable-frequency-train stimulation of skeletal muscle after spinal cord injury. *Journal of Rehabilitation Research and Development, 41* (1), 33-40.

Shepherd, R. B.(2001). Exercise and training to optimize functional motor performance in stroke: driving neural reorganization? Neural Plasticity, 8 (1-2), 121-129.

Shields, R. K. (1995). Fatigability, relaxation properties, and electromyographic responses of the human paralyzed soleus muscle. Journal of Neurophysiology, (73) 6, 2195-2206.

Shields, R. K., Dudley-Javorski, S., & Cole, K. R. (2006). Feedback-controlled stimulation enhances human paralyzed muscle performance. Journal of Applied Physiology,101(5),1312-1319.

Simpson, J. A. (1969). Terminology of electromyography. *Electroencephalography and Clinical Neurophysiology, 26,* 224-226.

Slade, J. M., Bickel, C. S., Warren, G. L., & Dudley, G. A. (2003). Variable frequency trains enhance torque independent of stimulation amplitude.Acta Physiologica Scandinavia,177,87-92.

Smith, G. V., Alon, G., Roys, S. R., and Gullapalli, R. P. (2003). Functional MRI determination of a dose-response relationship to lower extremity neuromuscular stimulation in healthy subjects. Experimental Brain Research, 150, 33-39.

Spriett, L. L., Soderlund, K., & Hultman, E. (1988). Energy cost and metabolic regulation during intermittent and continuous titanic contractions in human skeletal muscle. *Canadian Journal of Physiology & Pharmacology, 66* (2), 134-139.

Steele, D. S., & Duke, A. M. (2003). Metabolic factors contributing to altered Ca2+ regulation in skeletal muscle fatigue. *Acta Physiologica Scandinavia, 179* (1), 39-48.

Sullivan, J. E., & Hedman, L. D. (2004). A home program of sensory and neuromuscular electrical stimulation with upper-limb task practice in a patient 5 years after a stroke. Physical Therapy, 84 (11), 1045-1054.

**T**

Taylor, E., & Humphry, R. (1991). Survey of physical agent modality use. American Journal of Occupational Therapy, 45 (10), 924-931.

Taylor, J. L., Todd, G., & Gandevia, S.C. (2006). Evidence for a supraspinal contribution to human muscle fatigue. *Clinical and Experimental Pharmacology and Physiology, 33* (4), 400-405.

Terao, S., Takahashi, M., Li, M., Hashizume, Y., Ikeda, H., Mitsuma, T., & Sobue, G. (1996). Selective loss of small myelinated fibers in the lateral corticospinal tract due to midbrain infarction. Neurology, 47(2), 588-591.

Thomas, C. K. (1997a). Contractile properties of human thenar muscles paralyzed by spinal cord injury. *Muscle & Nerve*, *20* (7), 788-799.

Thomas, C. K., Bigland-Ritchie, B., Johansson, R. S. (1991) Force-frequency relationships of human thenar motor units. *Journal of Neurophysiology, 65*, 1509-1516.

Thomas, C. K., Butler, J. E., & Zijdewind, I. (2002). Patterns of pathological firing in human motor units. In S. C. Gandevia, U. Proske, and D. G. Stuart (Eds), *Advances in experimental medicine and biology* (pp. 237-244). New York: Kluwer Academic.

Thomas, C. K., Johansson, R. S., & Bigland-Ritchie, B. (1999). Pattern of pulses that maximize force output from single human thenar motor units. *Journal of Neurophysiology, 82* (6), 3188-3195.

Thomas, C. K., Griffin, L., Godfrey, S., Ribot-Cisar, E., & Butler, J. E. (2003). Fatigue of paralyzed and control thenar muscles induced by variable or constant frequency stimulation. *Journal of Neurophysiology, 89*, 202-204.

Thomas, C. K., Woods, J. J., & Bigland-Ritchie, B. (1989). Impulse propagation and muscle activation in long maximal voluntary contractions. *Journal of Applied Physiology, 67* (5), 1835-1832.

Thomas, C. L. (Ed.). (1997b). *Taber's cyclopedic medical dictionary* (18th ed.). Philadelphia: F. A. Davis.

Tong, R. K., Ng, M. F., Li, L. S., & So, E. F. (2006). Gait training of patients after stroke using an electromechanical gait trainer combined with simultaneous functional electrical stimulation. Physical Therapy, 86 (9), 1282-1294.

Tracy, B. L., Byrnes, W. C., and Enoka, R. M. (2004). Strength training reduces force fluctuations during anisometric contractions of the quadriceps femoris muscles in old adults. Journal of Applied Physiology, 96, 4, 1530-1540.

Tracy, B. L., and Enoka, R. M. (2006). Steadiness training with light loads in the knee extensors of elderly adults. Medicine & Science in Sports Exercise. 38, 4, 735-745.

**V**

Van Cutsem, M. V., Duchateau, J., & Hainut, K. (1998). Changes in single motor unit behaviour contribute to the increase in contraction speed after dynamic training in humans. *Journal of Physiology, 513,* 295-305.

Van Lunteren, F., & Sankey, C. B. (2000). Catchlike property of rat diaphragm: subsequent train frequency effects in variable-train stimulation**.** *Journal of Applied Physiology, 88*(2), 586-598.

Vigreux, B., Cnockaert J. C., & Pertuzon, E. (1980). Effects of fatigue on the series elastic component of muscle. *European Journal of Applied Physiology and Occupational Physiology, 45* (1), 11-17.

**W**

Wang, R. Y., Yang, Y. R. Tsai, M. W., Wang, W. T., & Chan, R. C. (2002). Effects of functional electric stimulation on upper limb motor function and shoulder range of motion in hemiplegic patients. *American Journal of Physical Medicine and Rehabilitation, 81* (4), 282-290.

Westerblad, H. & Allen, D. G. (2002). Recent advances in the understanding of skeletal muscle fatigue. *Current Opinions in Rheumatology, 14* (6), 648-652.

Westerblad, H., Duty, S., & Allen, D. G. (1993) Intracellular calcium concentration during low-frequency fatigue in isolated single fibers of mouse skeletal muscle. *Journal of Applied Physiology, 75* (1), 382-388.

Westerblad, H., Allen, D. G., & Lannergren, J. (2002). Muscle fatigue: Lactic acid or inorganic phosphate the major cause? News In Physiological Science, 17, 17-21.

**Y**

Yan, T., and Hui-Chan, C. W. (2005). Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial. Stroke, 36 (1), 932-933.

Yozbatiran, N., Donmez, B., Kayak, N., and Bozan, O. (2006). Electrical stimulation of wrist and fingers for sensory and functional recovery in acute hemiplegia. Clinical Rehabilitation, 20 (1), 4-11.

Yu, D. T., Chae, J., Walker, M. E., Kirstens, A., Elovic, E. P., Flanaga, S. R., Harvey, R. L., Zorowitz, R. D., Frost, F. S., Grill, J. H., Feldstein, M. and Fang, Z. P. (2004). Intramuscular neuromuscular electric stimulation for poststroke shoulder pain: a multicenter randomized clinical trial. Archives of Physical Medicine and Rehabilitation, 85 (5), 695-704.

**Z**

Zijdewind, C., Bosch, W., Goessens, L., Kandou, T. W., & Kernell, D. (1990). Electromyogram and force during stimulated fatigue tests of muscles in dominant and non-dominant hands. *European Journal of Physiology and Occupational Physiology, 60* (2), 127-132.

Zijdewind, I., & Thomas, C. K. (2003). Motor unit firing during and after voluntary contractions of human thenar muscles weakened by spinal cord injury. Journal of Neurophysiology, 89, 2065-2071

Zory, R., Boerio, D., Jubeau, M., & Maffiuletti, N. A. (2005). Central and peripheral fatigue of the knee extensor muscles induced by electromyostimulation. *International Journal of Sports Medicine, 26,* 847-853.

# Vita

Barbara Mollere Doucet was born in New Orleans, Louisiana, on December 4, 1961, the daughter of Barbara Barre' Mollere and Archie Joseph Mollere. After completing work at Hahnville High School in Boutte, Louisiana, in 1979, she entered Louisiana State University (LSU) in Baton Rouge, Louisiana, and received the degree of Bachelor of Science in Occupational Therapy from the LSU Health Science Center (LSUHSC) in New Orleans in 1984. During the following years, she was employed as an occupational therapist. She later entered graduate school at LSUHSC, completing the degree of Master of Health Science with an emphasis in Allied Health Education in 1996. She was then employed for several years as Assistant Professor of Clinical Occupational Therapy at LSUHSC. She began her doctoral work in 1998, attending Louisiana State University in Baton Rouge, Louisiana. She then moved to Texas, assuming the position of Rehabilitation Unit Manager at Presbyterian Hospital of Dallas in Dallas, Texas. She continued her graduate work at Texas Woman's University in Denton, Texas, and The University of Texas at Dallas, Texas. In August 2002, she entered the Graduate School of The University of Texas at Austin.

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